

ANNALS OF INTERNAL MEDICINE

SMS

1094

The American College of Physicians

VOL. 11 (OS, Vol XVI)

JULY, 1937

NUMBER 1

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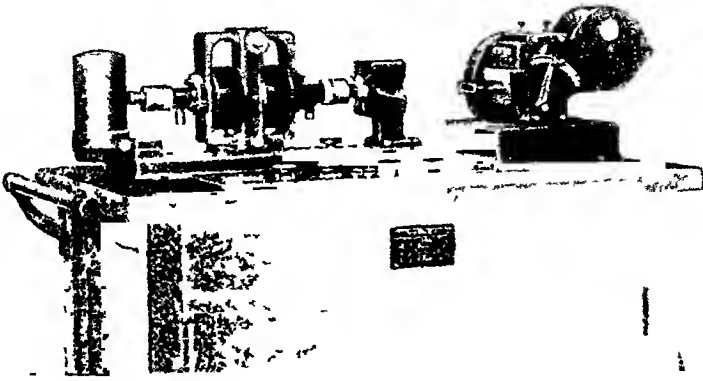


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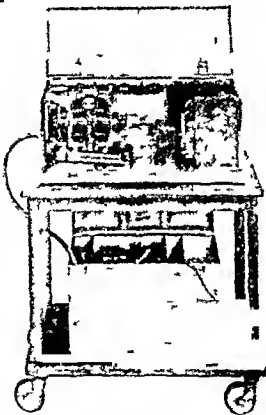
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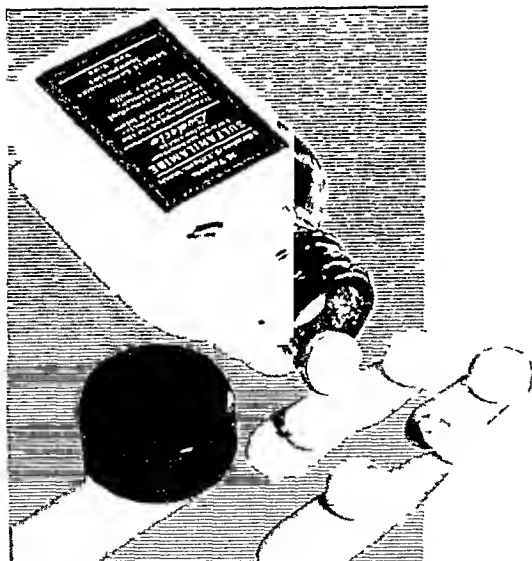
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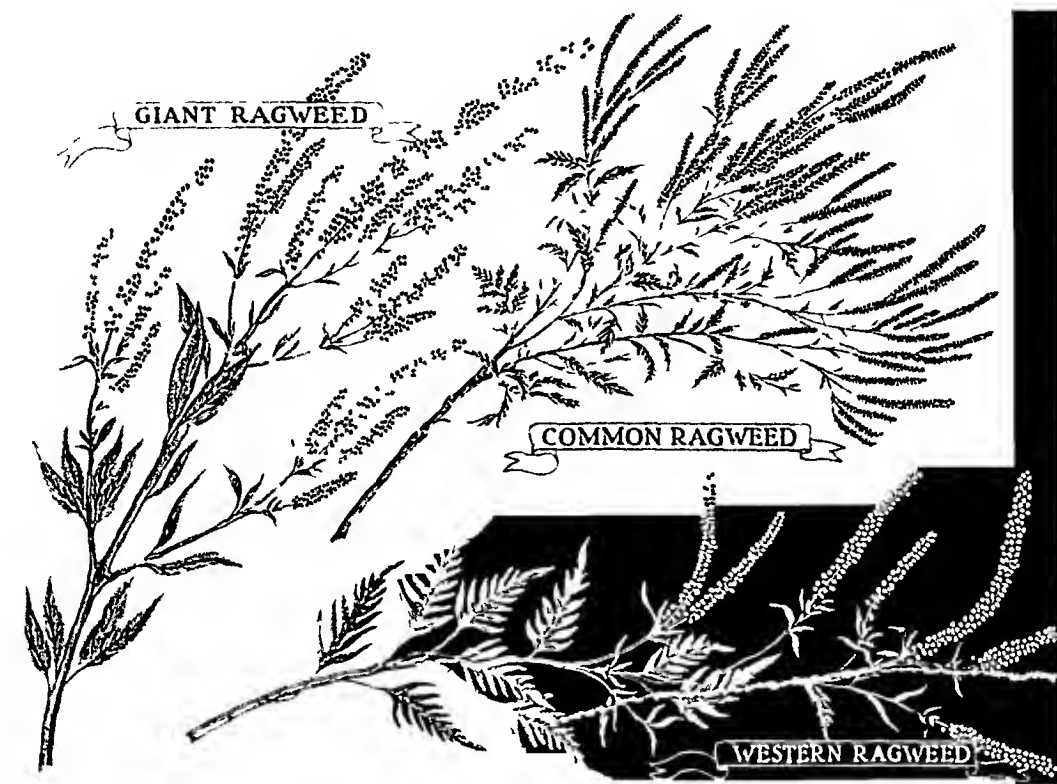
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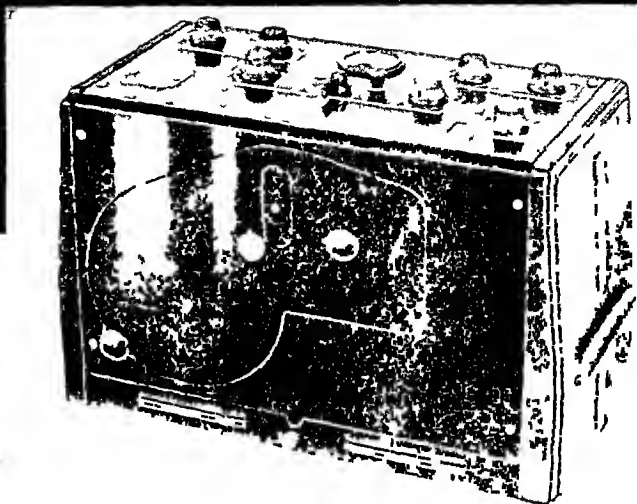
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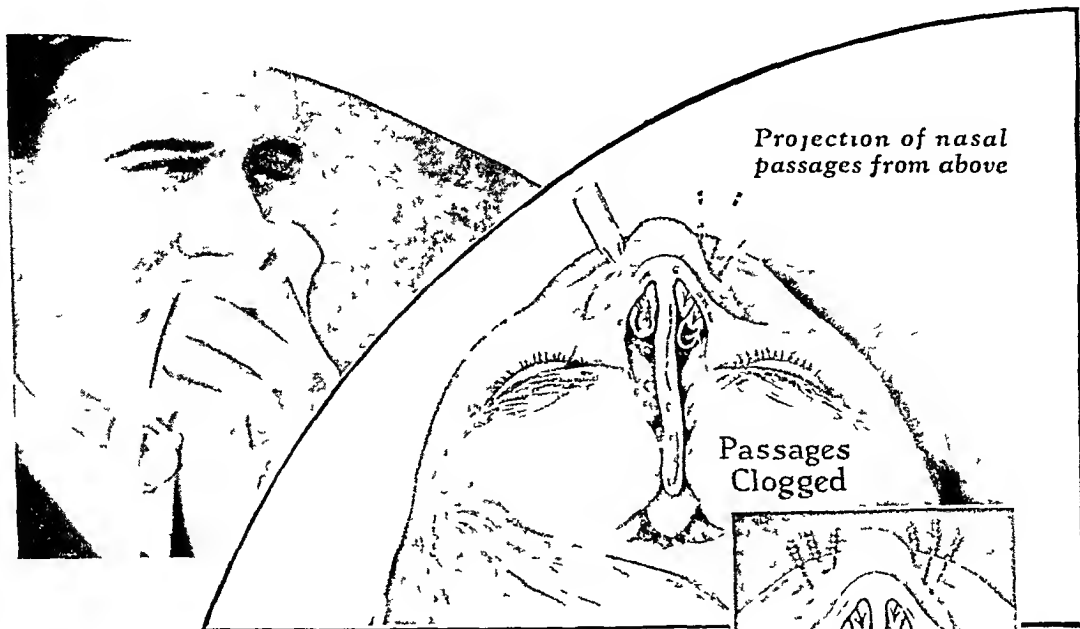


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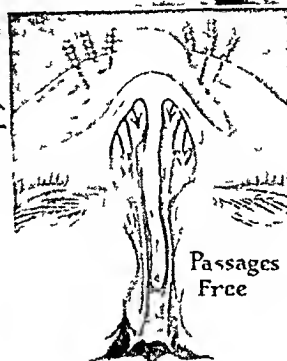
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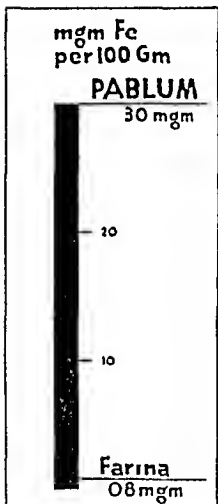
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ANNALS OF INTERNAL MEDICINE

VOLUME 11

JULY, 1937

NUMBER 1

RECENT KNOWLEDGE CONCERNING INFLUENZA

By RICHARD E. SHOPL, M.D., *Princeton, New Jersey*

FROM the time of Pfeiffer's announcement of its discovery in 1892¹ to 1918 *H influenzae* was quite generally regarded as the agent responsible for epidemic influenza. Because of this general belief, much of the huge volume of work done during the 1918-1920 pandemic was concerned with a further study of the relationship of this bacterium to the disease. The results obtained were confused and contradictory, some seemed to support the view that *H influenzae* was the cause of the pandemic disease, others opposed it. An unbiased review of the large literature on the subject leads to the conclusion that, while the question had still to be considered controversial, the claims for *H influenzae* as the causative agent of influenza were less convincing after the 1918 pandemic studies than they had been before.

Some of the opponents of the Pfeiffer bacillus theory suspected that the primary etiological agent of influenza might be a filtrable virus. Evidence for the virus theory obtained during the 1918-1920 pandemic was, however, extremely sketchy and unconvincing. A few investigators, notably Selter² and Leschke³ seem to have reproduced the disease in a small number of human subjects by spraying them with filtered respiratory tract secretions and washings from influenza patients. But against these apparently positive results must be placed the negative findings of other workers in much larger series of attempted infections. Kruse,⁴ Friedberger and Konitzer,⁵ Lister and Taylor,⁶ and McCoy, Rosenau et al.⁷ entirely failed to produce illness by spraying human subjects with filtered respiratory tract secretions from influenza patients. While it must be admitted that man is a bad experimental animal at best and practically useless when employed for experiment during an epidemic, it is apparent that, so far as published work is concerned, the evidence against a filtrable virus as the cause of influenza was more con-

* John Phillips Memorial Medal address presented at the St. Louis meeting of the American College of Physicians, April 21, 1937.

From the Department of Animal and Plant Pathology of The Rockefeller Institute for Medical Research, at Princeton, N. J.

vincing than that in favor of it. The conclusion seems warranted that, so far as experimental work done during the 1918-1920 pandemic is applicable, the theory that held influenza to be caused by a filterable virus was at least as highly controversial as the one which maintained the disease was caused by Pfeiffer's bacillus.

This much of a review of the older work on influenza has been necessary in order to prepare the way for an account of recently acquired knowledge concerning the disease. It is apparent to all, I believe, that one of the most serious handicaps under which earlier investigators worked was the lack of an experimental animal, other than man, susceptible to influenza. It is equally clear now that the recent increase in our knowledge of influenza has resulted largely from the discovery that certain of the experimental animals can be employed in studying the disease.

SWINE INFLUENZA

The statement that no animal except man acquires influenza under natural conditions is encountered frequently in the older medical literature. However, in the late summer or early autumn of 1918 a new disease which appeared among swine in the Middle West seemed to challenge this old contention. The new disease was not a sporadic and localized outbreak, actually millions of swine became ill and thousands died during the first few months of its prevalence. By October and November it was widespread among swine herds in Iowa and other parts of the Middle West. Dr. J. S. Koen, who first recognized the disease as being different from any previously encountered in swine, was so much impressed by the coincidental prevalence of human influenza and by the resemblance of the illness seen in man to that occurring at the time in hogs that he became convinced that the two were actually the same.⁸ He therefore gave the name "flu" to this new swine disease. The opinion of Koen that "flu" represented an entirely new swine epizootic disease, and that swine might have been infected in the first instance from man, was shared by some veterinarians and many farmers in the Middle West.⁹ Furthermore "flu" proved a generally accepted popular designation for the condition, though in the scientific literature it is usually referred to as "swine influenza." The disease has recurred each autumn, since its first appearance, in epizootics which vary from year to year in their severity and extent.

Now allowing for certain differences between swine and man, swine and pandemic human influenza were indeed very much alike. In addition to their coincidental prevalence in the autumn of 1918, the clinical and pathological pictures of the two diseases were similar. In both, fever, anorexia, cough and other signs referable to the respiratory tract were prominent, a leukopenia occurred in both diseases, and in both the degree of prostration was out of all proportion to the rest of the clinical picture. In both diseases the onset was sudden, the course short, and convalescence slow but usually uneventful. Both conditions appeared to be highly con-

tagious Death, when it occurred in either the human or swine disease, was frequently the result of a "water-logged," bloody, edematous pneumonia. It is, of course evident that all of these similarities could have been a matter of chance and that one is not warranted in drawing conclusions as to the relationship of the two diseases merely on the basis of clinical and pathological resemblances. Their etiological agents should be known and compared. In the beginning, or at the time that swine influenza gained prominence as a veterinary problem, a comparison of this nature was impossible because the causative agent of neither disease was known.

The etiology of swine influenza was finally determined in 1931 and it proved to be different in character from that of any hitherto known disease of animals or man. Instead of being caused by a single agent, swine influenza was found to result from infection with two such agents, one a virus, the other a bacterium, acting synergistically¹⁰. The virus differed from any previously known, and caused, when administered alone to swine, an extremely mild, indefinite, usually afebrile ailment, which, for want of a better name, was designated "filtrate disease". The bacterium was very similar to, if not identical with, the non-indol producing type of Pfeiffer's *H influenzae* and was named *H influenzae suis*¹¹. When administered alone to swine it proved non-pathogenic.

Here then in swine influenza was a bacterium like that believed by many to be responsible for influenza in man. Leaving out of consideration for the moment the possibility that *H influenzae suis* and *H influenzae* might play analogous rôles in their respective diseases, it was striking to find these similar bacteria closely associated with like diseases occurring in two animal species. The finding furnished additional evidence of a possible relationship between swine and human influenza. Furthermore, the demonstration that swine influenza was caused by the combined activity of this Pfeiffer bacillus-like organism and a filtrable virus made the suggestion obvious that the swine disease might actually be an etiological replica of human influenza. The thing lacking so far as the human disease was concerned, and this was quite important, was positive proof that a filtrable virus was present. Though long suspected, none had been conclusively or convincingly demonstrated. But there was not long to wait.

A FILTRABLE VIRUS IN HUMAN INFLUENZA

In 1933 Smith, Andrewes, and Laidlaw¹² transmitted a disease to ferrets by inoculating intranasally filtrates of pharyngeal washings from cases of epidemic influenza in man. The ferret disease proved to be serially transmissible, and was characterized by a two-day incubation period, a diphasic temperature response, symptoms of nasal catarrh, and variable systemic disturbances. The mucous membranes of the nasal passages of ferrets killed during the first or second febrile periods were acutely inflamed. In their original work, Smith, Andrewes and Laidlaw recovered the virus from the throat washings of five of eight cases tested and failed to recover it from

four subjects not suffering from influenza. Sera obtained from either recovered ferrets or from patients after an attack of influenza neutralized the virus. All the evidence first presented and that obtained later pointed to the etiological importance of this virus in the disease.

The presence of Smith, Andrewes and Laidlaw's virus in epidemic influenza has been amply confirmed. Francis recovered it from cases of the disease occurring in Puerto Rico,¹¹ Philadelphia,¹² Alaska,¹³ and New York¹⁴; Burnet isolated it from cases of influenza in Melbourne, Australia¹⁵; Brightman and Task found it in an outbreak among children in New Haven¹⁶; and Smorodintseff and his coworkers demonstrated its presence in an outbreak in Leningrad.¹⁷ Furthermore, Andrewes, Laidlaw and Smith, since their original discovery, have isolated a number of additional strains in England.¹⁸ It is evident that the virus is widely disseminated.

The strains of influenza virus thus far obtained from man have appeared to be identical with one another so far as could be judged by cross-immunity tests and by neutralization tests with sera from recovered animals.^{10, 11, 17, 18} However, Magill and Francis, using virus-neutralizing serum prepared in a non-susceptible host, have recently presented evidence that the Puerto Rico and Philadelphia strains differ antigenically.²¹ Since these differences were not detectable when sera from recovered susceptible hosts were employed in the cross-neutralization tests, it seems that, for practical immunological purposes, the influenza viruses isolated from patients in various parts of the world must still be considered serologically quite a homogeneous group.

ACTIVITIES AND PROPERTIES OF HUMAN INFLUENZA VIRUS

Production of Pneumonia in Ferrets. Francis¹² observed that, after several passages in ferrets anesthetized at the time of inoculation, the Puerto Rico strain of human influenza virus produced pulmonary consolidation in addition to the usual changes it had caused from the beginning in the upper respiratory tract. The pneumonias were of a bloody-edematous character and sometimes proved fatal. Similar passage of the original English strain resulted in its also acquiring the ability to produce pulmonary consolidation.²²

The Infection of Mice. About a year after the discovery that ferrets were susceptible to influenza virus, Andrewes, Laidlaw and Smith²³ and Francis¹³ found that the ferret-adapted virus was also pathogenic for white mice. Administered intranasally to etherized mice, a well-adapted virus caused illness which usually terminated fatally after from three to seven days. At postmortem the only constant changes were in the lungs. These were deep red and almost airless except for small emphysematous areas at the periphery.

Immunity Conferred by Infection. Influenza virus was found to confer immunity upon the animals it infected. Recovered ferrets were not only

solidly immune to reinfection but their sera contained neutralizing antibodies for the virus^{17, 21}

Cultivation and Size of Influenza Virus The size of the influenza virus particle has been estimated to be between 80 and 120 m μ on the basis of differential ultrafiltration through collodion membranes²⁵ and between 87 and 99 m μ as determined by centrifugation²⁶

The virus could not be cultivated upon ordinary bacteriological media although it grew readily in media containing minced chick embryo or upon the chorio-allantoic membrane of the developing hen's egg^{15, 27, 28} It is clear that, like other filtrable viruses, influenza virus requires living cells for its multiplication

COMPARISON OF THE VIRUSES OF HUMAN AND SWINE INFLUENZA

With the discovery of a virus in human influenza, the fortunes of the swine influenza virus took an unexpected turn It was found that the virus from swine was also pathogenic for ferrets and mice and that it caused a disease in these two animals which was indistinguishable clinically or pathologically from that produced by ferret-adapted human influenza virus^{12, 23 29 30} True, there were certain differences in the initial pathogenicity of the two viruses Thus, the swine influenza virus when administered intranasally to anesthetized ferrets induced pneumonia even in its first passage whereas the human virus required several serial passages in ferrets before it acquired the ability to cause pulmonary consolidation In like manner, swine influenza virus proved directly pathogenic for mice while the virus from man was pathogenic for mice only after it had been subjected to several serial transfers in ferrets^{*} It seems likely that these initial differences in the pathogenic activities of the two agents may be those due to "fixation" by prolonged sojourn in a foreign host since passage of human influenza virus through ferrets alters it in such a way that it becomes more like the swine influenza virus and less like the one originally obtained from man Human influenza virus, fully adapted to the ferret, produces a disease picture in ferrets and mice that is indistinguishable from that caused in these animals from the outset by swine virus

While influenza in swine is a disease of complex etiology and both the filtrable virus and *H influenzae suis* are essential to its causation, the disease in ferrets and mice appeared to be caused solely by the virus No evidence was obtained to indicate that *H influenzae suis* or any other bacterium modified the virus infection in these animals in any constant or significant manner^{12, 13, 23, 29, 30}

But the similarity between the swine and human influenza viruses did not end with their like pathogenicity for ferrets and mice It was found that they immunized against one another Thus ferrets or mice recovered from infection with swine influenza virus were not only immune to rein-

^{*} Francis and Magill have recently secured strains of influenza virus from man that "took" directly in mice without preliminary ferret passage¹⁶

fection with that agent but also usually resisted infection with the human influenza virus. In like manner, animals first infected with human virus were found later to be immune to the swine virus. Such cross-immunity suggested a close immunological relationship between the viruses from man and swine. That the two agents were not actually identical, however, could be shown by cross-neutralization experiments: they could be differentiated serologically.^{20, 20, 31} Each virus was completely neutralized by its homologous immune serum though the heterologous immune serum either failed to neutralize or neutralized only partially. The conclusion reached from consideration of cross-immunity and cross-neutralization experiments was that the viruses of human and swine influenza were related but not identical.

The swine influenza virus particle was found to have the same diameter as that of the human virus particle.²¹ Swine influenza virus was cultivable in media like that required by the human virus.^{21, 22}

THE SUSCEPTIBILITY OF SWINE TO HUMAN INFLUENZA VIRUS

The many similarities between human and swine influenza virus raised the question of whether the human agent might not be pathogenic for swine. This was studied experimentally first by Elkeles²³ and later by Shope and Francis.²⁴ It was found that swine, inoculated intranasally with human influenza virus alone, developed an extremely mild illness similar clinically and at autopsy to the flu-like disease caused by infection with swine influenza virus alone. When small amounts of a culture of *H. influenzae suis* were administered with the virus a more prostrating febrile illness usually resulted. This was similar to swine influenza although never so severe. At autopsy the pneumonia encountered was of the same character as that seen in swine influenza but much less extensive. The disease caused in swine by the human virus and *H. influenzae suis* could best be characterized as a mild swine influenza similar qualitatively but differing quantitatively from the typical disease occurring naturally in this species.

It was apparent from the work thus far described that the viruses of swine and human influenza were related but not identical. So far as our information went, the human virus, though capable of infecting swine, was probably specific for man, the swine virus was specific for swine.

But this view as to the species specificity of the two agents had to be modified when the influenza virus-neutralizing antibody content of human serum was studied.

ANTIBODIES TO HUMAN AND SWINE INFLUENZA VIRUS IN HUMAN SERA

Smith, Andrewes and Laidlaw^{1, 22} had shown that the sera of persons convalescent from influenza neutralized the human virus. Later Francis and Magill,²⁴ by comparing the antibody content of sera drawn during the acute stage of influenza with that obtained after recovery, demonstrated

that neutralizing antibodies for human influenza virus actually developed during an attack of the disease. From this it seemed likely that their presence in the serum of an individual was an expression of a previous infection with human influenza virus.

Sera from persons of different ages have been studied for their ability to neutralize human and swine influenza virus. The findings obtained in England by Andrewes, Laidlaw and Smith³⁰ and those gotten in this country by Francis and Magill⁴ and Shope³⁵ were in close agreement. Arranging the cases in three broad age groups it was found, in the English experiments, that the human virus was significantly neutralized by 62 per cent of the sera from persons over 20 years of age, by 57 per cent of the sera from people between 10 and 19 years old and by 33 per cent of the sera from children under 10 years. In the American experiments the human virus was completely neutralized by 48 per cent of the sera from individuals over 20 years of age, by 58 per cent of the sera from people between 10 and 19 years and by 49 per cent of the sera from children under 10 years. It can be seen from these data that, with the exception of the children in the English group, roughly half of the human sera studied neutralized human influenza virus. The incidence of antibodies encountered does not seem surprisingly high in view of the known recent widespread prevalence of the influenza virus.

But the results obtained in the corresponding experiments with swine influenza virus were unexpected. It was found, in the English experiments, that the swine virus was significantly neutralized by the sera from all persons over 20 years of age, by 66 per cent of the sera from individuals between 10 and 19 years but by none of the sera from children under 10 years. In the American experiments the swine virus was completely neutralized by 92 per cent of the sera from persons over 20 years of age, by 63 per cent of the sera from individuals in the 10 to 19 year age group but by only 11 per cent of the sera from children under 10 years. These results were surprising in two respects. First, it was unexpected to find that practically all adult human sera contained antibodies capable of neutralizing a virus that was supposedly specific for swine. Second, since the antibodies were so uniformly present in sera from adults it was surprising indeed to find that they were almost completely lacking in the sera of children. An interpretation of the significance of the findings was difficult because no strain of influenza virus immunologically like the one from swine had ever been recovered from man. The question will be considered more fully later.

DISCUSSION

In considering all of the work thus far done in determining the etiology of influenza in man one is struck by the fact that it can be divided both chronologically and by subject matter under most intense investigation into two main periods. During the first period which extended roughly from the 1889-1890 pandemic through the 1918-1920 pandemic, the interests of

investigators were largely bacteriological and were centered upon the problem of elucidating the rôle played by Pfeiffer's *H. influenzae* in the disease. During the second period which may be dated from the time of the discovery of a virus in the disease by Smith, Andrewes and Laidlaw up to the present, practically all investigative work has been focused upon the role played by this new virus. There has been very little overlapping in the subjects under most intensive study during each of these two periods.

Between the bacteriological and the virus periods of human influenza, investigation into the etiology of swine influenza revealed this disease to be caused by the concerted action of a bacterium like Pfeiffer's bacillus and a filtrable virus. Not only was the swine bacterium like Pfeiffer's bacillus, but experience with it during the first three years' work, in attempting to determine its etiological relationship of swine influenza, closely paralleled the experience investigators of human influenza had had with Pfeiffer's bacillus during the bacteriological period^{11, 16}. The arguments for and against considering *H. influenzae suis* etiologically important in swine influenza were much the same as those already debated for many years regarding the causal role played by *H. influenzae* in human influenza. Furthermore, the viruses of swine and human influenza were subsequently found to be strikingly alike though not identical. Here then, in the etiology of swine influenza, was what seemed to be a connecting link between the two periods of human influenza investigation—a compromise between Pfeiffer's bacillus on the one hand and a filtrable virus on the other which accepted both as etiologically essential.

But is it justifiable to apply knowledge gained in the study of swine influenza to human influenza? An answer to this question depends partly upon the significance assigned to the swine influenza virus-neutralizing antibodies found in human sera. Two hypotheses to explain the presence of these are apparent. One would interpret them as specific, the other as non-specific, in the sense that, respectively, they had or had not resulted from past infection with swine influenza virus. The non-specific hypothesis will be considered first.

It is known that experimental animals repeatedly exposed to human influenza virus sometimes develop antibodies capable of neutralizing both the human and the swine viruses¹¹. Perhaps the swine virus antibodies in human sera were non-specific in the sense that they had been established not by virtue of previous infection with swine influenza virus but rather had resulted from repeated previous exposures to human influenza virus. If this were the correct explanation then all human sera which neutralized the swine virus should also neutralize the human agent. Comparison of duplicate tests against the two types demonstrated clearly that this was not the case: antibodies neutralizing swine virus were frequently present in human sera which failed to neutralize human virus. In these it was evident that the neutralizing antibodies for swine influenza virus had not resulted from previous infection with human virus, unless one chose to believe that the

specific antibodies for the human virus disappeared after each influenzal infection while the non-specific swine virus antibodies persisted and were gradually built up by each succeeding attack of influenza. There are as yet no data to indicate that this conjecture is likely or even possible.

The hypothesis which interprets the swine virus-neutralizing antibodies in human sera as specific and to have resulted from past infection with a virus whose antigenic composition was similar to that of swine influenza, just as the human virus antibodies are considered to reflect a past infection with human influenza virus, is more in harmony with the facts determined by animal experimentation. On the basis of this interpretation it is apparent that human sera contain neutralizing antibodies for at least two immunologically distinct types of influenza virus. One is the current human virus of Smith, Andrewes and Laidlaw known to be widely prevalent in man at the present time. The other, antigenically like swine influenza virus, is unknown and has never been detected in man. It has, however, left ample evidence of its past widespread prevalence in the form of neutralizing antibodies in the sera of almost all adult human beings. That it is no longer widely existent in the human population is indicated not only by the failure of investigators to recover it from cases of influenza during the past four years, but by the almost complete absence of antibodies for it in the sera of children. If one ascribes a specific character to the swine virus-neutralizing antibodies in human sera, the conclusion that this unknown human virus was indeed swine influenza virus, or a closely related agent, is inescapable.

However, there is no direct evidence that the swine influenza virus, as we know it today, is capable of infecting man. Indeed, indirect evidence indicates that it does not infect man because, while swine influenza has occurred annually since 1918, our serological evidence suggests that the human prototype of swine influenza virus ceased infecting man generally 10 or more years ago.

The most apparent interpretation of these findings is that the swine virus represents a surviving form of an extinct or temporarily quiescent human influenza virus which has become so "fixed" in swine as to be no longer pathogenic for human beings. If this is the case, then the history that swine influenza appeared for the first time in 1918 serves to date the time of prevalence of this vanished human virus. The experimental and historical facts seem best explained, for the present at least, by the theory that the swine influenza virus represents a surviving form of that pandemic in man in 1918, as already suggested by Laidlaw³⁷. On this basis, the presence in human sera of antibodies neutralizing swine virus would be considered to indicate that the donors of these sera had undergone immunizing exposures to, or infections with, an influenza virus of the 1918 pandemic type. Thus it seems possible that swine influenza may represent more than merely an interesting analogue of the human disease, it may actually bear a relationship to pandemic influenza.

The matter of determining the relationship between the influenzas of swine and man is of importance only in so far as it bears upon the question of the etiology of the human disease. The causative agents of the swine disease are known. Furthermore, agents of a similar nature are present in the human disease. Do these agents play the same rôle in pandemic human influenza that they are known to play in swine influenza? I have purposely, in this paper, called attention to the close similarity that exists between the disease pictures of influenza in swine and pandemic influenza in man, to the suggestive history that swine influenza made its first known appearance during a great human pandemic, to the apparent identity of the predominant bacterium in the human disease with the one known to be etiologically essential in the swine disease, to the close relationship between the viruses of human and swine influenza, and to the presence in human sera of neutralizing antibodies for both the human and swine viruses. Any one of the parallelisms might be fortuitous, it seems unlikely that all should be.

The possibility must, of course, be kept in mind that human beings may resemble ferrets and mice more closely than they do swine in their reaction to influenza virus. In this event the virus would be considered the sole and primary etiological agent of influenza and any associated bacteria would be thought of as merely concomitant and of secondary importance. However, the disease caused in ferrets and mice by the human influenza virus alone may be just as highly artificial in reflecting the complete etiology of human influenza as is that caused in the same animals by swine influenza virus alone in reflecting the complete etiology of the swine disease. It remains to be determined whether pandemic influenza in man is a disease like that in ferrets and mice caused by infection with the virus alone or whether it resembles swine influenza and requires both the virus and a bacterium. Personally, I am of the opinion that the virus of human influenza, like that of swine influenza, constitutes only a partial etiology of the disease in which it is involved and that workers of the bacteriological period who contended for the etiological importance of Pfeiffer's bacillus may have been at least partially right.

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CLINICAL INVESTIGATIONS OF INSULINS WITH PROLONGED ACTIVITY

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A YEAR ago, at the meeting of the American College of Physicians, Dr Joslin expressed the opinion that Hagedorn by effectively retarding the action of insulin with protamines had opened a new era in the treatment of diabetes. During the past year hundreds of physicians have had the opportunity to use protamine insulin in the treatment of diabetes, and I am informed that their verdict is almost unanimously favorable. In February of this year an improved modification of Hagedorn's preparation was placed on the market. It already had received the official endorsement of the Insulin Committee in Toronto and that of the Council on Pharmacy and Chemistry of the American Medical Association.

I propose in this paper to recount certain clinical investigations which illustrate some of the peculiarities of the action of insulins with retarded activity, and in part explain the advantages attending their use.

A pitfall to be avoided when studying the effect in diabetes of drugs and diets, is the trial of the remedy in cases in which the diabetes is of short duration. This mistake in the past has led to a number of erroneous conceptions, the notions, for instance, that dark breads can be tolerated better than white breads and that honey and maple sugar are less harmful than other sweets. Quackery in diabetes thrives because of the tendency for spontaneous remission in the early course of this disease. Tolerance for carbohydrate improves during the first year or two, if only minor attention is paid to limiting the intake of carbohydrate, and the credit is given, undeservedly, to the medicine used or the special food. The patients who kindly consented to serve as subjects for these clinical investigations had had diabetes for five years or longer.

Mild diabetes also can mislead the observer, by fluctuating in intensity. Furthermore arteriosclerosis and certain other complications of diabetes sometimes decrease the sensitivity of the patient to overdoses of insulin, and under these circumstances enough unmodified insulin may be administered in one injection to prevent hyperglycemia for 24 hours. Because of this fact we chose patients who were hypersensitive to overdoses of insulin, they previously had been more or less refractory to satisfactory control, and most of them were "pedigreed," in the sense in which Dr Woodyatt has used this term, that is, they had been studied before, some of them many times, so that the characteristics of their disease were known.

* The Trimble Lecture, Medical and Surgical Faculty of the State of Maryland, Baltimore, Maryland, April 28, 1937, also presented in part to the American College of Physicians, St. Louis, Missouri, April 19, 1937, under the title "Protamine and Other Long-Acting Insulins."

The work to be presented represents the combined efforts of several of us. My associates include Drs Edwin J Kepler, Edward H Rynearson and Jesse Bollman, and the following Fellows of The Mayo Foundation for Medical Education and Research: Randall C Sprague, Benjamin B Blum, Bertha M Davis Clark, Reid R Heffner, Clarence W Erickson, James A Barr, Donald W Ingham and George R Crisler. For the necessarily arduous analytical work we are indebted to Dr Arnold E Osterberg and members of his department, and for much assistance our thanks are due to Miss Mary A Foley, Sister Mary Victor, Sister Rebecca and others in the dietetic and nursing departments of the St Mary's and Kahler hospitals. The preparation of protamine insulin came from the Eli Lilly Company of Indianapolis, the crystalline insulin was supplied by Stearns and Company of Detroit.

THE PROLONGED ACTION OF PROTAMINE INSULIN

Our first observation revealed that the claim for prolongation of action of protamine insulin was fully warranted (figure 1). A woman aged 49

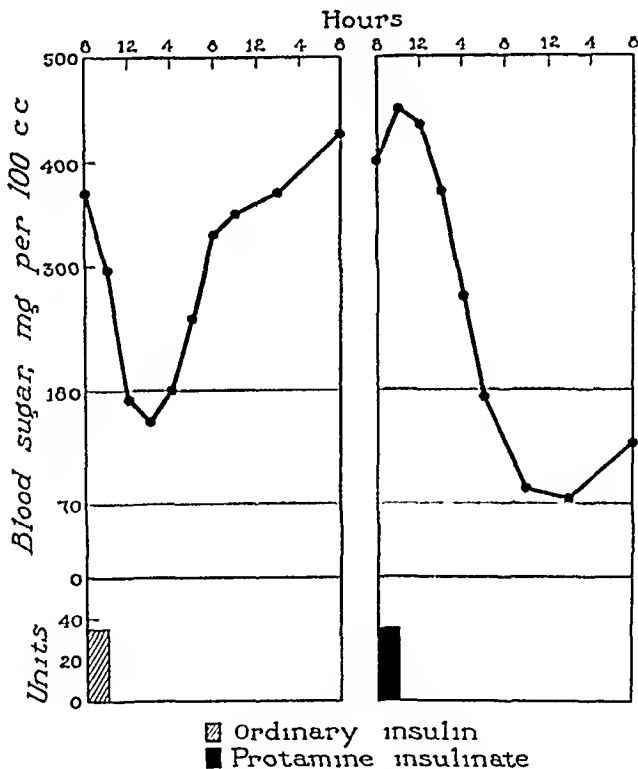


FIG 1 Comparative duration of action of ordinary insulin and protamine insulin

years, who had had severe diabetes for nine years, was given 35 units of unmodified insulin 20 minutes before breakfast. The breakfast contained 30 gm of carbohydrate, 18 gm of protein, and 44 gm of fat. The level of the blood sugar fell from its fasting value of 370 mg per 100 cc and

reached a minimum of 150 mg per 100 c c in six hours. The noon and evening meals were withheld, and no more insulin was used. The value for the blood sugar rose as rapidly as it had fallen. By the following morning it stood at 425 mg per 100 c c and the value for the carbon dioxide combining power of the plasma was 28 volumes per cent. One cannot say with certainty at just what hour, in this observation, the action of the insulin terminated, because a blood sugar time curve is an expression of several variables. However, it is reasonable to regard the point at which the curve rose above the renal threshold for dextrose (about 180 mg) as marking the end of the action of insulin. By this arbitrary standard, the 35 unit dose, in this case, acted for eight hours.

On another day, with conditions as nearly identical as possible, an equal dose of plain protamine insulin was followed by an increase in the value for the blood sugar after breakfast from 400 to 449 mg per 100 c c. Then a prolonged fall occurred. The low point, 72 mg per 100 c c, was reached 18 hours after the injection, and the next morning there still was evidence of the activity of insulin. The value for the blood sugar then was only 148 mg per 100 c c, and glycosuria and evidence of acidosis were absent.

This observation, and others to be described, led us to anticipate that protamine insulin might be given in one dose each 24 hours. Especially should this be possible if the injection was made in the morning, so that the peak effect would come at the proper time to be buffered by the hyperglycemic effect of food eaten during the day. We put this plan of treatment to trial, and soon were convinced of its desirability. The same plan has been adopted in Toronto and elsewhere. The convenience to the patient of being able to take in the morning all the insulin he needs for the day is not inconsiderable. In milder cases protamine insulin alone has been used, in more severe cases a supplementary dose of an insulin with prompter action has been necessary.

COMPARATIVE ACTION OF PLAIN, CALCIUM, AND ZINC PROTAMINE INSULINS

Soon after the introduction of protamine insulin it became apparent that the stability of the precipitate would have to be increased before it could be made available commercially. Suspensions of the original preparation, after standing for several days, would lose some of their potency, due to adherence of the precipitate to the sides of the bottle. The manufacturers overcame the difficulty by adding small amounts of soluble salts of calcium (1 or 2 mg of calcium per 100 units) or of zinc (1 mg of zinc per 500 units). The additions, it was found, also changed the duration of action of the insulin. Calcium shortened the period of action, while zinc had the opposite effect. Zinc also formed a more stable precipitate. It is for these reasons it now is regularly incorporated in the preparation which has been placed on the market.

The relative intensity and duration of action of protamine insulin with and without additions of calcium or zinc are illustrated (figure 2). The subject of these observations was a girl, aged sixteen years, who had been diabetic for 10 years and required about 80 units of unmodified insulin daily. In each observation 50 units of the preparation to be studied were injected and food was withheld for the next 48 hours. Between each study the patient was treated for several days with unmodified insulin, the last dose being given 14 hours before the start of the next injection of a protamine preparation. Thus, a high value for the fasting blood sugar was insured, and the durations of action of the various preparations could be compared under similar conditions. At the forty-eighth hour after the administration

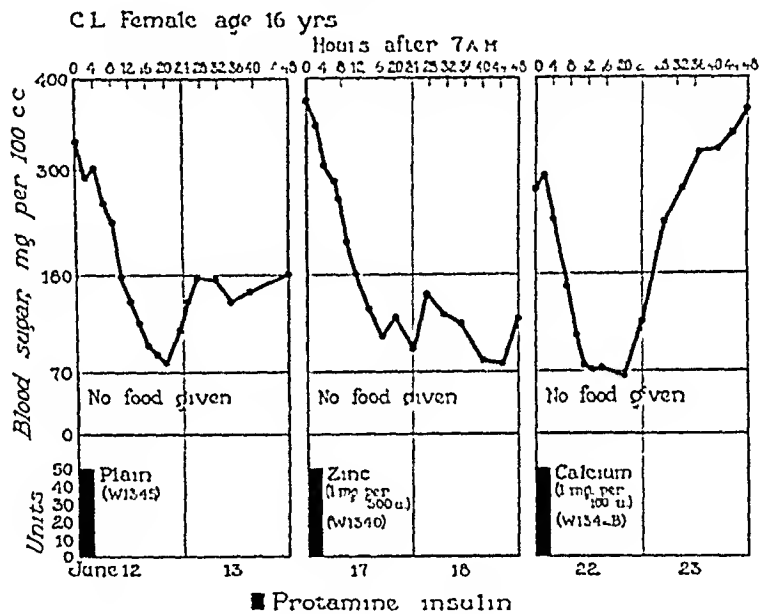


FIG. 2. Comparative duration of action of plain, calcium, and zinc protamine insulins.

50 units of plain protamine insulin, activity was almost spent, the blood sugar curve had risen to the renal threshold. At the forty-eighth hour after the administration of an equal dose of protamine insulin containing 1 mg of zinc per 500 units, the value for the blood sugar was still near minimal point, which was evidence of continued strong action of insulin. When 50 units of the preparation containing 1 mg of calcium per 100 units were given, the value for the blood sugar passed the renal threshold by the twenty-eighth hour.

STUDIES OF PROLONGED HYPOLYCAEMIA

Many a diabetic, using unmodified insulin, has had insulin reactions during his sleep, with only a headache or sore muscles or a bitten tongue the following morning to inform him of the episode. The spontaneous recovery

attributable to the fact that the action of unmodified insulin is spent in a relatively few hours and hepatic glycogenolysis begins as soon as the insulin is exhausted. The prolonged action of protamine insulin made it seem possible that a resulting hypoglycemia might not be recovered from spontaneously, and we became apprehensive for patients who, using protamine insulin, might fail to get their food. An attack of migraine, for instance, might interfere with the retention of food and have serious consequences. Therefore, the duration and severity of the hypoglycemia produced by protamine insulin in patients who fasted were made the subject of investigation.

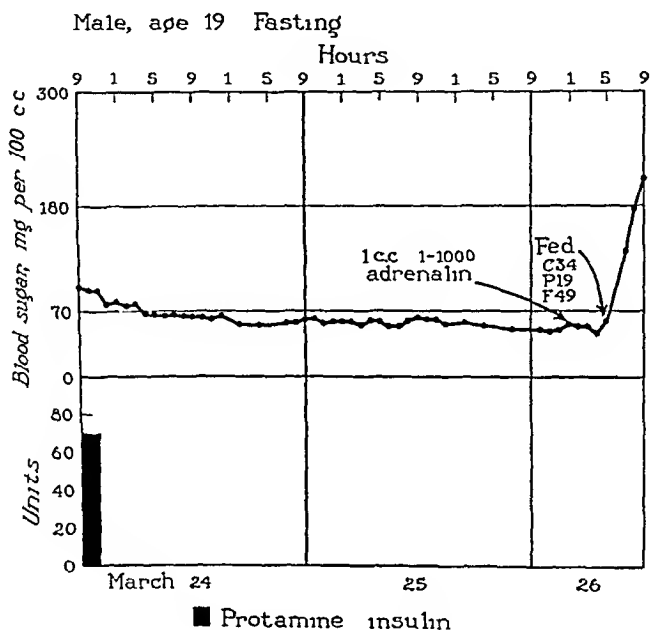


FIG 3 Prolonged hypoglycemia from administration of protamine insulin to a fasting diabetic subject

In one study (figure 3) a young man, who had been a diabetic for six years, received 70 units of plain protamine insulin. This dose previously had been given every morning and was what was required to prevent glycosuria. The value for the blood sugar at the time was 94 mg per 100 cc. It fell gradually to a low level of 45 mg and remained between 45 and 62 mg for the last 38 hours of a fast of 57 hours. There were no notable symptoms until late. In the fifty-second hour the patient became restless and irrational, the tendon reflexes were exaggerated, the pupils were dilated, and the value for the systolic blood pressure rose to 150 mm of mercury from previous readings of about 120 mm. The condition of the patient was much improved 10 minutes later by the injection of 1 cc of a 1:1000 solution of epinephrine, although the values for the blood sugar, determined at intervals of 15 minutes after administering the epinephrine, had not changed significantly. The fast was terminated in the fifty-seventh hour because of the reappearance of symptoms.

This observation, and others like it, showed that when hypoglycemia is produced very gradually it may not be attended by the stormy symptoms characteristic of the reactions to unmodified insulin. Subsequent experience has confirmed this conclusion. If a patient rests in bed, after overdoses of protamine insulin, symptoms may be absent entirely or appear very late. If he is up and about they are more likely to be manifest because exercise provokes them. As a rule, however, they differ from those with which patients and physicians, using unmodified insulin, have become familiar. The phenomena which probably have been attributed correctly to a protective mobilization of epinephrine are less pronounced. The value for the blood sugar falls so gradually that the suprarenal glands are not aroused. Therefore, tremor, sweating, tachycardia and pounding pulses usually are missing, and their place is taken by symptoms of cerebral origin, such as lassitude, fatigue, headache or nausea.

It appeared from studies like the one I have cited (figure 3) that loss of consciousness was less likely to occur after the use of protamine insulin, and that hypoglycemia could be tolerated for many hours without serious consequences. This was reassuring. However, symptoms of cerebral irritation were apparent before the termination of the fast, and we have found (Bollman) that dogs made hypoglycemic for several days with protamine insulin would die of convulsions when dextrose was given to restore them. Multiple petechial hemorrhages were scattered throughout the brains of these animals. Therefore, it was not to be concluded that long-continued hypoglycemia was harmless, and we were led to recommend that patients take sugar at intervals of half an hour if meals were missed or whenever unusual symptoms suggested overdosage. Experience later revealed that hypoglycemia may return after treatment or even after meals, and therefore the patients were advised that the doses of sugar administered at intervals of half an hour were to be resumed if the symptoms returned.

THE EFFECT OF THE TYPE OF DIET ON THE CONTROL OF GLYCOSURIA

There has been much difference of opinion as to what type of diet gives the best results in the practical management of diabetes. Many physicians have followed the recent trend toward allowing relatively large amounts of carbohydrate. Others have adhered to the principles established by Naunyn, and are keeping the intake of carbohydrate low. Others have taken the middle road, planning diets with greater reference to general nutritional considerations.

Two young men, aged 18 and 20 years respectively, who had diabetes of maximal severity, were given first low and later high carbohydrate diets and single morning injections of protamine insulin (figure 4). In each case the loss of dextrose in the urine was considerably greater after administration of the high carbohydrate diet than it was after administration of the low carbohydrate diet, as was the average of the five blood

sugar determinations made each day. The average level of the morning blood sugar, on the other hand, was lower during the days on which the high carbohydrate diets were administered. These postabsorptive levels were so low, indeed, that it was impossible without provoking reactions to use larger doses of protamine insulin in an attempt to control the daytime hyperglycemia and glycosuria. This and other experience has dissuaded us from resorting to diets containing more than about 150 gm of carbohydrate when patients are treated with protamine insulin. Some patients,

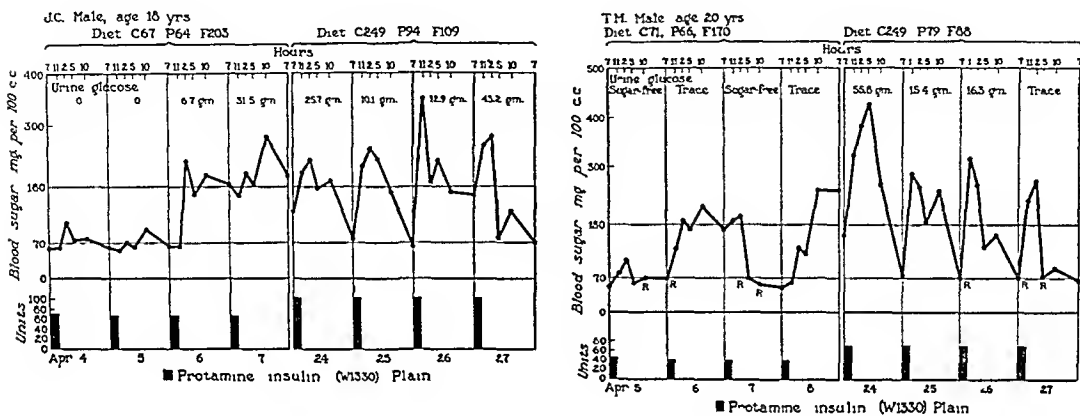


FIG 4 Comparative effect of low and high carbohydrate diets in patients treated with protamine insulin

however, do well with more liberal amounts, as is illustrated by the following observation (figure 5)

A diabetic woman, aged 47 years, who required 50 units of protamine insulin on a measured diet containing 140 gm of carbohydrate, was given 60 units a day and served food from the general kitchen. Only candy and table sugar were withheld. On the first day of the general diet, 14.2 gm of sugar were excreted in the urine, but on the days that followed there was never more than a trace of sugar. This patient probably represented the type of adult diabetic whose blood sugar is not easily depressed below normal levels by unnecessarily large amounts of insulin. On the basis of the result, it would appear that in cases of the insulin-insensitive type of diabetes greater latitude in the amounts and quality of food may be permissible with the use of protamine insulin. Subsequent experience has confirmed this conclusion, although this type of treatment is not recommended.

OBSERVATIONS OF THE ACTION OF CRYSTALLINE INSULIN

About a year ago announcement was made of prolonged hypoglycemic action obtained with solutions of crystalline insulin. Since then, other reports have led to the assumption that the action of this crystalline insulin is comparable to that of protamine insulin. Our experience is different. We have been supplied with the material through the courtesy of the in-

ventor of a commercial method for its production, and our studies show that while its action is longer than that of unmodified insulin it is not long enough to permit treatment of severe diabetes with fewer injections than two a day. The preparation cannot take the place of protamine insulin, on the other hand, either this preparation, or one with a similarly intermediate duration of action, would be useful as an adjunct in the treatment of certain diabetic patients.

I already have stated that when diabetes is severe, sugar often appears after meals unless supplementary, quick-acting insulin is given with the morning dose of protamine insulin. The degree of glycosuria observed under these circumstances may be harmless, but until we have proof of its harmlessness we must insist on its control. This means using supplementary insulin, and for this purpose an insulin with action like that of

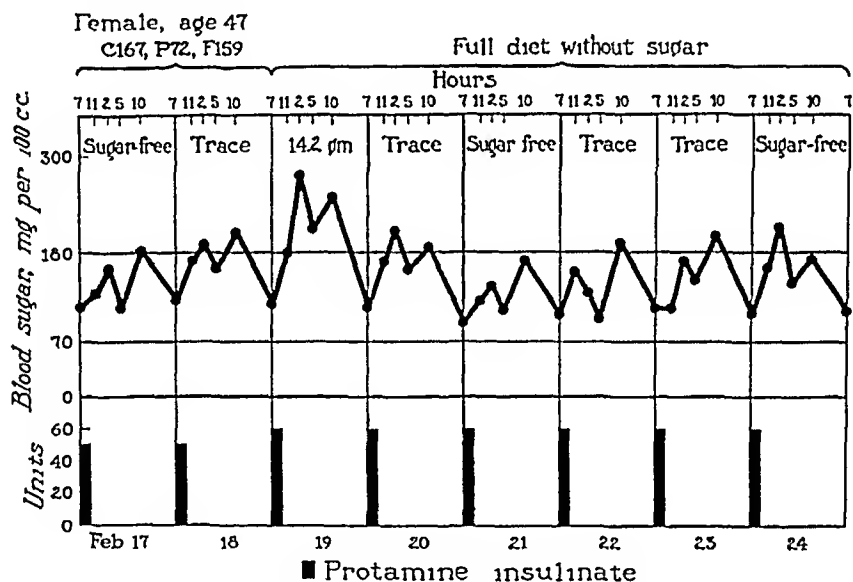


FIG 5 Treatment with unrestricted diet and protamine insulin

crystalline insulin would be very useful. Ordinary unmodified insulin is not satisfactory because its action is spent too early. The preparation of crystalline insulin that we have studied represents exactly what is needed. Its action is long enough so that when it is injected in the morning, together with the dose of protamine insulin, it amplifies the hypoglycemic effect during the day and prevents glycosuria after meals. By evening, however, its action has been spent, and thus the hypoglycemic effect of the protamine insulin is not exaggerated during the night.

An ideal insulin would be one which combined the activity of the right dose of protamine insulin with that of the right dose either of crystalline insulin or a preparation of similar behavior. Unfortunately, a good many difficulties stand in the way of achieving this. One patient would require more of the quick and less of the slow action, while another would need

more of the slow and less of the quick action. Such an insulin, therefore, would have to be "tailor-made" for the individual, as Dr. Campbell has suggested. A more likely solution of the difficulty may be expected from the preparation of a protamine insulin to which a quick-acting insulin can be added as required. At present, protamine insulin contains an excess of protamine, and thereby unmodified insulin which is added to it is precipitated. Possibly a way can be found to overcome the necessity for this excess. Until then, if supplementary doses of quick-acting insulin are to be given, the patient must take these separately, using a clean syringe for each injection.

I am showing data bearing on the duration of action of preparations of crystalline insulin, partly because of the interest in this subject and also because these data provide other information of practical significance in the treatment of diabetes.

An experiment I have described (figure 1), in which a single dose of insulin was given in the morning followed by breakfast but no other meals, was repeated several times to determine the relative duration of action of crystalline and protamine insulin. The volunteer diabetic patient who served in the first study of this type also consented to serve as the subject of these later studies. Before each observation she was maintained with unmodified insulin for a period of three days to avoid any holdover effects from previous injections of protamine insulin. In each observation the dose of insulin was the same, 35 units, and the breakfast always consisted of 30 gm. of carbohydrate, 19 gm. of protein and 44 gm. of fat. It represented the breakfast of her maintenance diet.

In the observation of January 11 to 12, the insulin used was a solution of a special crystalline insulin. The blood sugar time curve is shown in figure 6. The data reveal that the insulin was spent before the twentieth hour. By the twenty-fourth hour signs of impending acidosis were present. In the observation of January 15 to 16 (figure 6) protamine zinc insulin was used in the same dosage (35 units). This produced an equal degree of hypoglycemia, more tardily, but maintained the blood sugar at a low level until after the twenty-eighth hour. Also, no sugar appeared in the urine until the fortieth hour, and there were no signs of acidosis until the forty-fourth hour.

These data illustrate what I have said, namely, that the action of the crystalline preparation is retarded considerably more than is that of unmodified insulin, but that the retardation of crystalline insulin is not comparable to that of protamine insulin.

PROTEIN WASTAGE PREVENTED WITH PROTAMINE INSULIN

In an observation made January 22 to 23, the patient who had been the subject of the observations of January 11 to 12 and January 15 to 16 was given 35 units of the preparation of crystalline insulin used before. In-

stead of a breakfast, however, followed by prolonged fasting, she received food every two hours. The feeding consisted of a mixture of milk and cream, so arranged that each feeding would supply amounts of carbohydrate, protein and fat comparable to a twelfth of the amounts of these food factors in the maintenance diet. The data are recorded in figure 7. It was observed that the duration of hypoglycemia did not exceed 12 hours, that sugar appeared in the urine by then, and that after 16 hours the excretion of nitrogen was greatly increased.

The observation made on January 22 to 23 was repeated February 5 to 6, with a preparation of crystalline insulin to which zinc had been added (figure 8). The course of events was almost the same as it had been before, although the action of the insulin was intensified slightly and con-

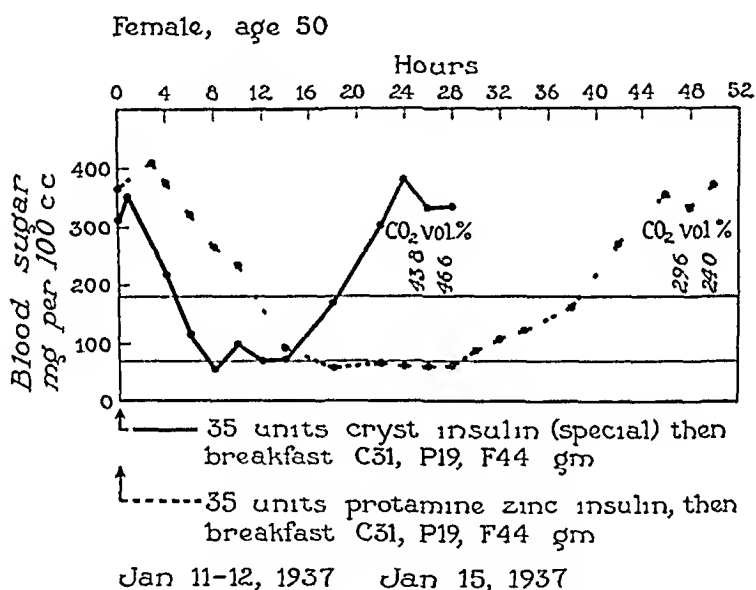


FIG. 6 Comparative duration of action of a special crystalline insulin and protamine zinc insulin

tinued about four hours longer. Even so, evidence of insulin activity had passed by the sixteenth hour. The value for the blood sugar was increased, the urine contained sugar and the excretion of nitrogen was increased.

Attention is invited to the behavior of the metabolic balance for nitrogen in these studies. The inflow of the nutrient at a continuous rate, accomplished by feeding the mixture of milk and cream at two-hour intervals, and the collection of urine at intervals of exactly four hours, made it possible to obtain this balance for a succession of four-hour periods. The patient at the beginning of each study had been given no insulin for 14 hours, and that insulin was unmodified insulin. No long-acting insulin had been used for several days, and since the case was one of severe diabetes, insulin action at the beginning of each study probably was minimal.

The negative balance for nitrogen of the first four-hour period in both studies is accounted for, I believe, by this circumstance. The sparing effect on protein of insulin given at the beginning of each study was not evident until after the first period. This delay is readily explained by the time necessary for absorption of the insulin. The effect of this insulin shows itself in the diminished excretion of nitrogen in the second, third and fourth periods. As the observations proceeded, a time was reached in each study when the excretion of nitrogen again rose and a negative

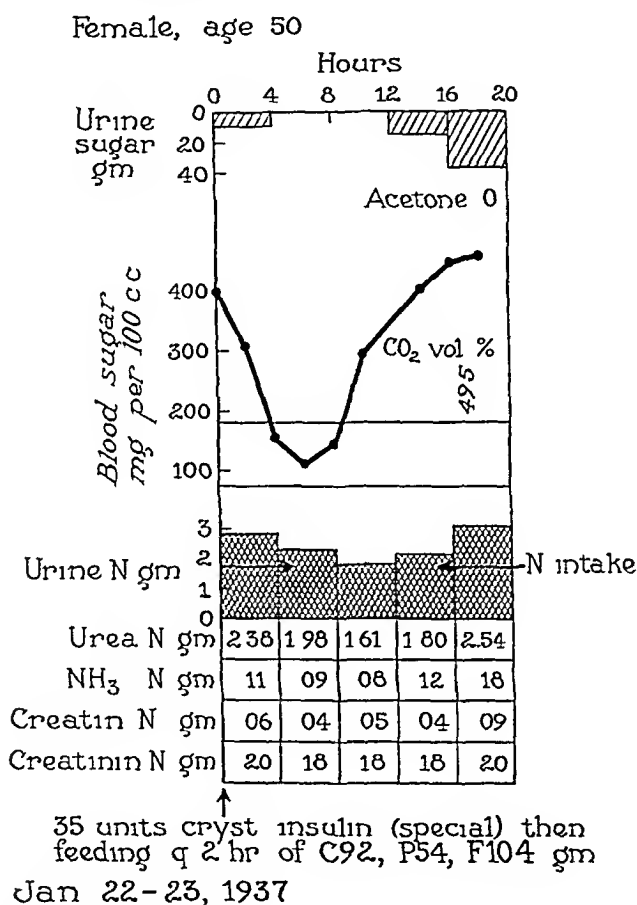


FIG 7 Negative nitrogen balance before and after period of activity of a dose of crystalline insulin

balance again was observed. This time coincided roughly in each case, with the time when the blood sugar curve rose above the renal threshold for dextrose.

The behavior of the balance for nitrogen in these studies would have escaped detection except for collection of the urines in four-hour periods, and the analysis of these separately for their content of nitrogen. Examinations of 24 hour collections would not have indicated negative balances for nitrogen, for the reason that the loss of nitrogen during the periods when

insulin was inactive would have been offset by the retention of nitrogen in the other periods

Negative balances for nitrogen have long been observed in cases in which severe diabetes is out of control, the condition formerly was called "azoturia," but so far as I know, it has not been demonstrated before that azoturia occurs so soon after the period of activity of a preceding dose of insulin. The phenomenon is not without practical importance. Patients treated with unmodified insulin are commonly given one dose before each

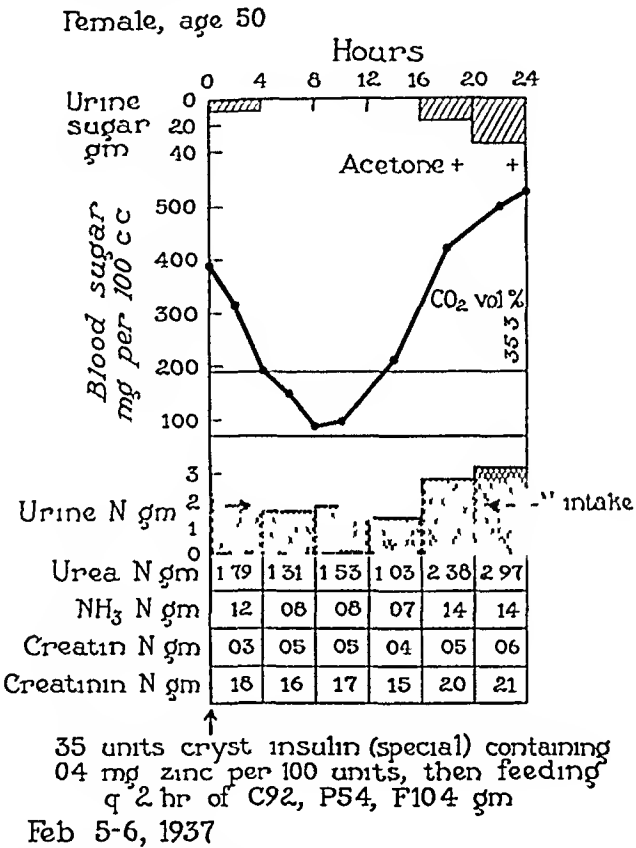


FIG 8 A longer period of activity was imparted to crystalline insulin by the addition of zinc, negative nitrogen balances occurred before and after period of insulin activity

meal, or two doses, one before breakfast, the other before supper. The time of action of unmodified insulin is not more than eight hours, and under these circumstances the balance for nitrogen may become negative for one or more short periods in each 24 hours. In these periods the protein of the body is subjected to drainage of its amino-acids to supply material out of which the liver can manufacture sugar. Intracellular as well as deposit-protein may be drawn upon, to judge from the increased excretion of creatine and creatinine which was observed when the balance for nitrogen was negative in the studies mentioned (figures 7 and 8)

It has been a common observation of those who have had experience with protamine insulin that patients receiving preparations of it gain in strength and fitness. Improvement has been noticeable, particularly in individuals who previously, using unmodified insulin, were not perfectly controlled. It is not always possible with protamine insulin to obtain complete control in cases of severe diabetes, but even when the control with protamine insulin is imperfect the patients say they feel better, and gradual improvement in tolerance for carbohydrate may be observed. I suggest that the reason for the improved sense of well-being of such patients and the improvement in their tolerance may be attributable to the avoidance of intermittent periods of azoturia.

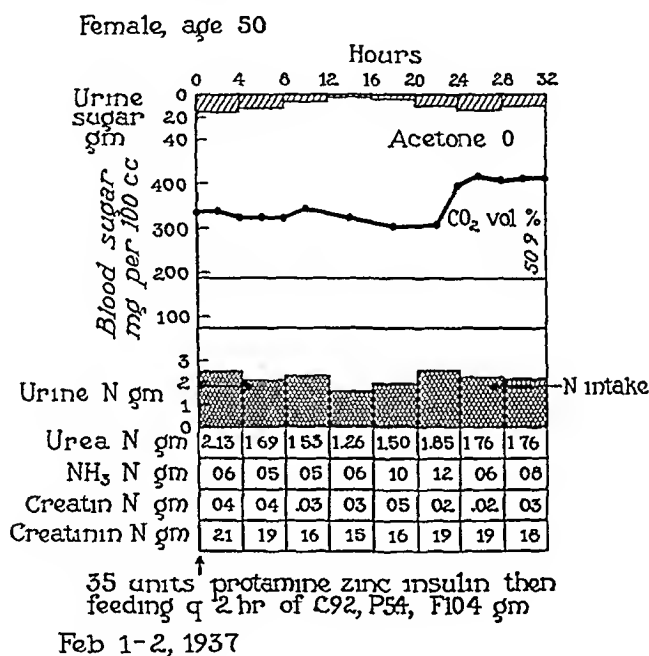


FIG 9 A dose of protamine zinc insulin, which was too small to control glycosuria, prevented significant loss of nitrogen for 32 hours

This hypothesis is supported by the following evidence. In an observation made February 1 to 2 (figure 9), planned exactly like those of January 22 to 23 and February 5 to 6, protamine zinc insulin was given. The same patient submitted to the observation and the number of units of insulin which were administered was the same. Again, a negative nitrogen balance was observed in the first four-hour period. The amount of protamine insulin was not enough to lower the blood sugar below the level at which it was found in the morning. It, therefore, was inadequate to suppress glycosuria and yet the excretion of nitrogen was depressed after the first four hours, it remained below the level of the intake of nitrogen until the end of the twentieth hour. The balance was still not grossly negative even after 31 hours.

Similar data were obtained in another study. The patient in this case was a young woman who had diabetes of extreme severity. It antedated the introduction of Banting's insulin. Protamine insulin containing calcium was given in two observations (figure 10 and 11) and zinc protamine insulin was given in a third (figure 12). A protein sparing effect was evidenced each time by diminished excretion of nitrogen after the first period. With the preparations containing calcium the sparing effect lasted for only 24 hours, but with the preparation containing zinc it was still apparent in the period between the thirty-second and thirty-sixth hours. In this last

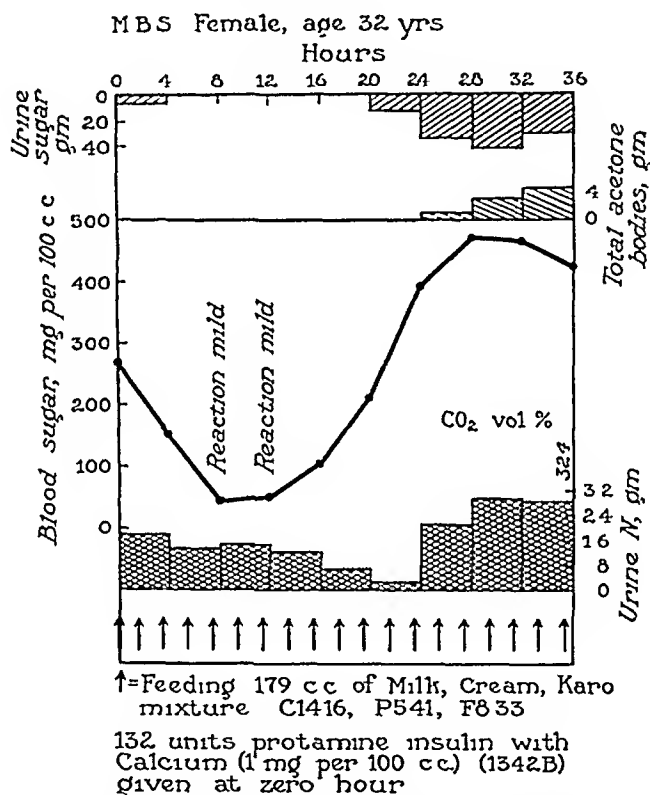


FIG. 10 An injection of protamine insulin with added calcium inhibited excretion of nitrogen for 24 hours, the period of activity was followed by azoturia

period the value for the blood sugar stood at almost as high a level as it had in the beginning of the experiment, and 16 gm of sugar were excreted in the urine.

The results of these observations also bear on the question I raised before, whether glycosuria after meals is harmful when patients are treated with protamine insulin. They show that moderate glycosuria under these circumstances is not attended with azoturia, which may mean that such glycosuria is not as harmful as that which occurs in intervals between the periods of activity of doses of unmodified insulin. The prevention of pe-

moderate azoturia by the use of protamine insulin may even mean that those degenerative disorders which so frequently complicate diabetes—retinitis, neuritis, and arteriosclerosis—will occur less frequently, or if present, will develop less rapidly, but more time must pass before this can be determined.

PROTAMINE INSULIN IN THE TREATMENT OF DIABETIC ACIDOSIS

A final topic demanding brief mention is the use of protamine insulin in the treatment of diabetic acidosis. It was the general belief a year ago

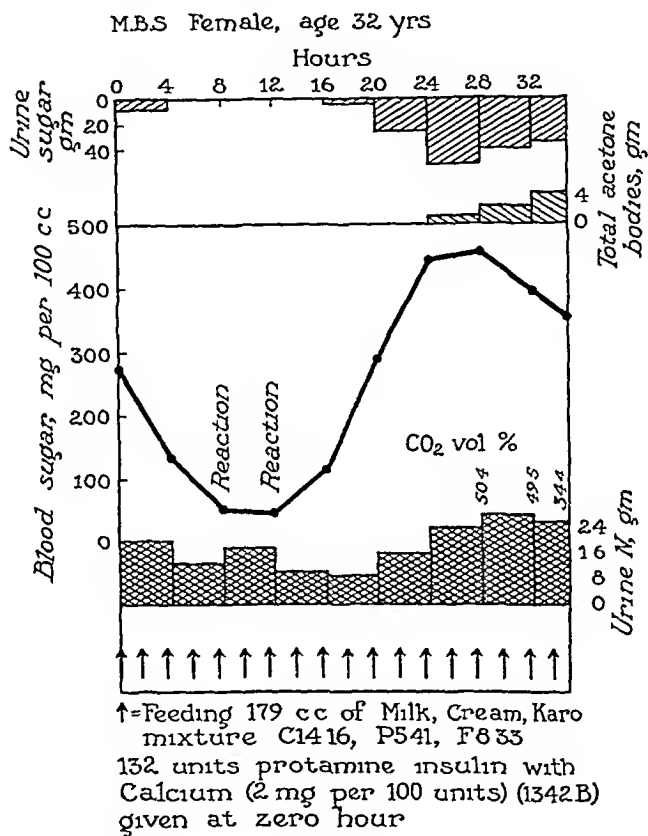


FIG 11 An injection of protamine with added calcium inhibited excretion of nitrogen for 24 hours

that the retarded action of the new insulin made it undesirable for use in emergencies. My associates and I now are convinced that this opinion is mistaken, and that a dose of protamine zinc insulin used together with quick-acting insulin, is of advantage. A report of some of our experiences with this has already been made by Kepler, Ingham and Crisler. The slow absorption of protamine insulin guarantees a continuous supply of insulin to the circulation. Thus, continuous action is effected no matter how rapidly insulin may be exhausted after it enters the circulation. A continuous insulin effect is difficult to obtain in acidosis by injecting unmodified insulin.

at intervals such as usually are chosen, for the reason probably that insulin after its absorption is destroyed more rapidly than usual. Our practice now is to give protamine insulin at the beginning of treatment, in a dose of from 50 to 100 units, and thereafter to treat the patient in the conventional manner with the multiple doses of unmodified insulin that are suggested by frequent tests of the blood and urine. We have treated seven patients who had diabetic acidosis, in this way, and the results have been surprisingly satisfactory. The doses of unmodified insulin found necessary in all but one case have been much smaller than expected, the time required to restore

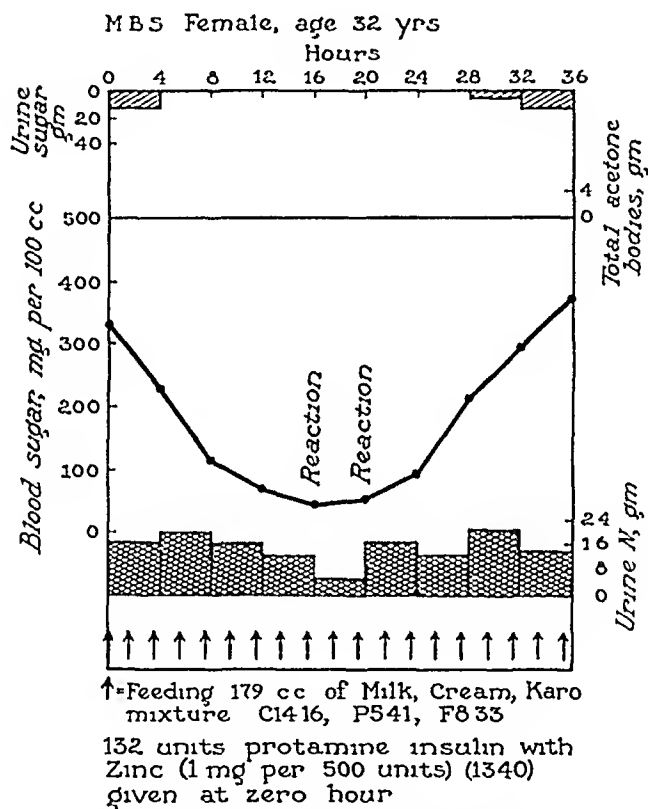


FIG 12 An injection of zinc protamine insulin inhibited loss of nitrogen for 36 hours, despite the hyperglycemia and glycosuria which occurred after the twenty-eighth hour

the patient has been shortened, and the period of continued insensitivity to insulin, which usually is encountered after attacks of acidosis, has been avoided. Possibly we have had a series of unusually favorable cases, but I am quite sure this is not the entire explanation. The patients in two instances were in profound coma.

The data in the last case of acidosis, at this writing, are shown (table 1). The patient was 59 years of age. The recent statistical data on diabetic acidosis reported from the clinic by Dr. Baker and from the Deaconess Hospital by Dr. Joslin and his associates, show a mortality of about 40 per

TABLE I
Treatment of Diabetic Acidosis

	March 17 1937					March 18 1937				March 19 1937				March 20 1937			
	a m		p m			a m		p m		a m		p m		a m		p m	
	9 30	11 00*	2	5	10†	8	11‡	4	10	7	11	4	10	7	11	4	10
<i>Blood</i>																	
Sugar, mg per 100 c c	594	540	306	136	54	297											
CO ₂ combining power, volumes per cent	17 4	13 5	31 5	46 6	57	57											
<i>Urine</i>																	
Sugar, grade	4			4			4	3	4	2	0	1	0	0	0	0	0
Acetone, grade	3			3			0	0	0	0	0	0	0	0	0	0	0
<i>Insulin, units</i>																	
Protamine	100						40			40				30			
Unmodified	50	30	10				10			10							

* Urea 72, sodium 299, potassium 20.4, calcium 10.6, chlorides 300, sulphates 5.8, phosphorus 6.0 mg and protein 8.8 gm, per 100 c c of blood plasma or serum. Began administration of 0.9 per cent sodium chloride (2000 c c given in 3 hours). Sodium bicarbonate, 5 per cent, intravenously (300 c c given in 1 hour). (300 c c of the solution of sodium bicarbonate left in stomach after lavage)

† Began administration of orange juice at 2-hour intervals (650 c c given in 10 hours)

‡ Diet started. Carbohydrate 140, protein 59, and fat 119 gm

cent for patients in the sixth decade who require treatment for acidosis. Diabetes had been present for five years and the dose of insulin had been 40 units daily (two injections daily, each of 20 units of unmodified insulin). The attack was precipitated by the failure of the patient to take insulin. I am thankful to say that she was not a graduate of our diabetic school. She accompanied a relative and was not intending to consult us about herself. She became fatigued on a Sunday, by a long automobile journey, was disinclined to eat supper and omitted the dose of insulin. She was nauseated on Monday, and omitted meals and insulin. She took 20 units of unmodified insulin on Tuesday morning, but none that evening. She began to vomit during the night, and on Wednesday morning called a physician. She was drowsy on admission to the hospital, but not unresponsive. Her breath smelled strongly of acetone and the respiration was markedly hyperpneic. The skin and tongue were dry. Extreme thirst and abdominal pain were the chief complaints. The balance of the story is told by the data in the table. Suffice it to add that this patient was so well by the fifth day that no amount of insistence could dissuade her from leaving the hospital.

SUMMARY

Selected observations have been presented to illustrate some of the peculiarities of the action of preparations of protamine and crystalline insulins. Conclusions based on these and other studies are as follows:

The activity of protamine insulin is prolonged for more than 48 hours

in fasting diabetic patients. The period of activity of unmodified insulin is less than 12 hours in fasting patients.

Further prolongation of action has been effected by the amount of zinc contained in the preparation of protamine insulin recently placed on the market. The addition of calcium shortens the duration of activity.

Symptoms may be absent for many hours in fasting patients who are made severely hypoglycemic by the administration of protamine insulin. When symptoms finally appear they are likely to be limited to those of cerebral origin, such as lassitude, fatigue, headache, and nausea.

Greater instability of the level of the blood sugar adds to the difficulties of treatment with protamine insulin, when much carbohydrate is included in the diet. This may not be true in cases of the type of diabetes characterized by insensitivity to overdoses of insulin.

The duration of action of solutions of previously crystallized insulin is intermediate. It does not extend beyond 12 or 14 hours when patients receive food. The duration of action of protamine insulin when food was given exceeded 36 hours.

The experimental data presented illustrate the importance of insulin in protecting the proteins of the body from catalysis. They reveal, furthermore, that in severe cases of diabetes, azoturia and creatinuria were only restrained during the period of activity of the dose of insulin injected. Therefore, it appears that when exclusive dependence is placed on multiple doses of an insulin which has an action of short duration, intervals may occur in each 24 hours when the balance for nitrogen will be negative. If unmodified insulin is used this can only be prevented by spacing doses more closely than has been customary. Such periodic intervals of azoturia are not encountered when an insulin is used which has an activity extending for more than 24 hours, and I have suggested that the continuous protection of the proteins of the tissues affected by this means may account for the improved healthiness and apparent gain of tolerance of patients using protamine insulin.

Finally, I also have directed attention to the usefulness of protamine insulin in the treatment of diabetic acidosis. Here again, its value seems to depend on the continuity of the insulin activity obtained.

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THE HEMOPOIETIC LIVER PRINCIPLE

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THE hemopoietic liver principle is also known as the anti-pernicious anemia principle and the erythrogenic liver principle. As you are aware, the interaction in the gastrointestinal tract of an as yet unidentified constituent of the gastric juice, called the "intrinsic factor," with some dietary component associated with protein, known as the "extrinsic factor," forms a third substance which is absorbed via the portal circulation and stored in the liver where it is very likely further elaborated. This substance, the hemopoietic liver principle, is then released to the bone marrow where it brings about the normal maturation of the red blood cells from the megaloblastic to the normoblastic stage. The term, anti-pernicious anemia principle, implies that the substance is pharmacologic rather than physiologic in character. Furthermore, the principle is effective in the treatment of various macrocytic, hyperchromic anemias other than pernicious anemia. The term, erythrogenic liver principle, is too limited inasmuch as the substance also appears to stimulate the formation of granulocytes and thrombocytes, as well as the maturation of the red blood cell. Hence the term, hemopoietic liver principle, appears to me to be the most appropriate. In this discussion, I shall deal briefly with some features of the chemistry, bioassay physiology and pathological physiology of the hemopoietic liver principle.

Since the demonstration of the effectiveness of liver in pernicious anemia by Minot and Murphy ¹ in 1926, the chemistry of the hemopoietic liver principle is being slowly unfolded. As a result of the early work of Cohn and his coworkers ² in 1927 leading to the preparation of a potent liver extract suitable for oral administration, it became apparent that the hemopoietic principle was relatively heat-stable, soluble in water and 70 per cent ethanol, relatively insoluble in 95 per cent ethanol, and insoluble in ether. In 1928 Cohn ³ further purified his liver extract so that 0.6 gm per day orally was as effective as 250 gm of whole liver in the treatment of pernicious anemia. At this time, Cohn considered the active principle to be either a nitrogenous base or a polypeptide. In 1930, Gansslen,⁴ Cohn,⁵ and Castle⁶ prepared liver extracts of sufficient purity to be administered parenterally. Cohn then regarded the hemopoietic liver principle as a secondary or tertiary amine. In 1935, Dakin and West⁷ prepared the principle in such form that 80 mg parenterally was effective in producing a remission in pernicious anemia patients. They considered the active principle to be a complex consisting of an aminohexose or glucosamine and certain amino-acids. Pyrimidine and purine bases were absent according to them. In the same year,

* Presented at the St. Louis meeting of the American College of Physicians, April 22, 1937.

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Fiske and his coworkers⁸ reported that the hemopoietic principle was probably a combination of L-tyrosine, a complex purine, and a third unidentified fraction. In 1936, Dakin and his collaborators⁹ modified their previous conception somewhat and reported that the principle was a peptide containing arginine, leucine, glycine, proline, hydroxy-proline, aspartic acid, and an acid resembling hydroxy-glutamic acid. In the same year, Wilkinson¹⁰ reported the preparation of the principle in such form that 18 mg. was sufficient to produce a remission in pernicious anemia and Strandell, Laland and their coworkers^{11, 12} stated that they had a product which was effective in the astoundingly small dose of 0.7 mg. Neither of these groups of investigators gave any data on their conceptions of the chemical structure of the hemopoietic principle. The chemistry of the principle, therefore, is still unsettled, although as indicated, there has been considerable progress. Very little is known about the chemistry of the two precursors of the hemopoietic principle. The intrinsic factor of the gastric juice is probably enzymic in nature, it is heat-labile, and otherwise different from the liver principle.¹³ The so-called extrinsic factor of the dietary likewise has not been identified chemically as yet but it is known to be relatively heat-stable and to be associated with protein, especially that of beef muscle, autolyzed yeast eggs, rice polishings, wheat germ, and liver.¹⁴ Although it was once thought that the extrinsic factor was vitamin B₁₂ (G), this is now definitely known not to be the case.^{15, 16}

Since the hematogenic liver principle cannot be tested for chemically, preparations thought to contain it must be assayed biologically. Up to the present, the only satisfactory assay subject is the untreated pernicious anemia patient showing a red blood cell count of 3,000,000 or less.¹⁷ After a control period of 1 to 7 days, the material to be tested is administered during a 10-day interval and daily reticulocyte counts together with erythrocyte, hemoglobin and leukocyte determinations every two to three days are made. The presence of satisfactory quantities of the hemopoietic liver principle in the preparation assayed is shown by a temporary reticulocytosis reaching its peak on the fifth to the eighth day and an accompanying or succeeding increase in erythrocytes and hemoglobin. The minimum reticulocyte response to be expected with a potent preparation is to a certain extent inversely proportional to the original level of the red blood cells. The standard minimum reticulocyte responses are as follows: for a level of 1,000,000 red blood cells per cu. mm., 30 per cent, 1,500,000, 18 per cent, 2,000,000, 12 per cent, 2,500,000, 7 per cent, and 3,000,000, 4 per cent. However, during the past few years, the use of this method of clinical assay has become increasingly difficult owing to the scarcity of untreated patients with pernicious anemia. Moreover, work on the chemistry and physiology of the hemopoietic principle and on the pathogenesis of pernicious anemia and other macrocytic, hyperchromic anemias has been greatly impeded. Hence numerous attempts have been made to devise a suitable laboratory method of bioassay. Of the many procedures proposed, the so-called guinea

pig,^{18, 19} rat,²⁰ and pigeon²¹ methods have received most attention. Each of these depends upon the production of a significant reticulocytosis in normal members of these species by the administration of material containing the hemopoietic liver principle. The validity of each of these methods has been questioned especially on the ground that the reticulocytoses regarded as significant are actually within the limits of normal variability. Certainly the magnitude of the reticulocyte increases regarded as significant by the proponents of the guinea pig and rat methods are very small. Recently we have modified the original pigeon method in such a way as to overcome the objections which have been raised against it.²² Unfortunately, however, we have found that the reticulocytosis produced in pigeons by the hemopoietic liver principle is not specific for this substance. This same objection of non-specificity applies equally forcibly to the guinea pig and rat methods. Our modification of the pigeon method, however, is of definite value as a negative test and further work with liver preparations of known effectiveness or ineffectiveness in pernicious anemia may well show it to be of value in a positive way as well. The ideal laboratory bioassay procedure, of course, involves the production of experimental pernicious anemia, or at least a readily obtainable, chronic, and reasonably severe macrocytic, hyperchromic anemia in animals. Although I shall speak later of experimental macrocytic, hyperchromic anemias produced in animals, difficulties of a practical or other nature appear to preclude the utilization of any of those produced thus far for assay purposes.

Having considered the chemistry and bioassay of the hemopoietic liver principle, we now pass to a consideration of certain facts known concerning its physiology and pathological physiology. Subsequent to the demonstration by Minot and Murphy of the effectiveness of liver in the treatment of pernicious anemia, Castle and his coworkers²³ in 1928 showed that whereas normal human gastric juice mixed with beef muscle was, like liver, effective in the treatment of pernicious anemia when administered orally, a mixture of beef muscle and gastric juice from patients with pernicious anemia was ineffective. Despite some contradictory findings, subsequent work by others has amply confirmed Castle's conclusion that by the interaction of the so-called intrinsic factor of the gastric juice and the so-called extrinsic factor of the dietary, there is formed in the upper gastrointestinal tract of the normal individual a third substance which is absorbed by way of the portal circulation and stored in the liver. From there, probably after further elaboration, the hemopoietic principle is released by way of the blood and passes to the bone marrow to exercise its characteristic effect in facilitating the maturation of the red blood cells from the megaloblastic to the normoblastic stage. Due to the comparative absence of the intrinsic factor in the gastric juice in pernicious anemia, the physiologic process just outlined is grossly deficient and as a consequence normal hematopoiesis is depressed with the resulting macrocytic, hyperchromic anemia, granulopenia, and thrombopenia characteristic of this disease. Whereas normal hog dog

beef, and human livers have been shown to contain appreciable quantities of the hemopoietic principle, the livers of untreated or inadequately treated pernicious anemia patients have been found to be devoid or nearly so of this substance^{24, 25}. Obviously, if the physiological cycle outlined for the hemopoietic liver principle is correct, interference with its normal sequence in other ways should result in a macrocytic, hyperchromic type of anemia. (1) Thus one might expect that gastrectomy would lead to a pernicious anemia-like blood-picture. However, complete gastric resection in the rat,²⁶ hog,^{27, 28} dog,²⁹ and monkey³⁰ has led only to a mild microcytic, hypochromic anemia in the hands of all investigators except one,³¹ although the amount of the hemopoietic principle in the liver of the hog has been shown to decrease following gastrectomy.^{7, 12} The explanation of these essentially negative results is not entirely clear but the fact that the intrinsic and extrinsic factors have been shown to be present not only in the wall of the stomach but also in the wall of the duodenum^{32, 33} and probably the jejunum, ileum,³⁴ and colon of the hog may well be important in this connection. On the other hand, a macrocytic, hyperchromic anemia resembling that of pernicious anemia develops in a definite percentage of humans subjected to complete gastrectomy for carcinoma or other causes and is relieved by the administration of the hemopoietic liver principle.³⁵ (2) A lack of the extrinsic factor in the diet should result in a deficiency of the hemopoietic liver principle. Thus far the difficult task of devising a diet free of the extrinsic factor and feeding it to animals has not been reported. However, a vitamin B₁₂ deficient diet which was probably also deficient in the extrinsic factor, has been shown to produce a macrocytic anemia in approximately half of the hogs to which the diet was given. Moreover, the intrinsic factor was reported to have disappeared from the gastric juice of the anemic animals.³⁷ A macrocytic anemia in monkeys on a vitamin B₁₂ deficient diet, probably lacking in the extrinsic factor, has also been reported.³⁸ Clinically a dietary lacking in the extrinsic factor appears to be one of the factors involved in the genesis of the macrocytic anemia which may occur in sprue.³⁹ It is likely also that a deficient intake of the extrinsic factor is responsible for tropical macrocytic anemia, in which treatment with either the extrinsic factor or the hemopoietic liver principle is effective.⁴⁰ (3) Deficient absorption of the product of the interaction of the intrinsic and extrinsic factors should also produce a blood-picture resembling pernicious anemia. Experimentally, a macrocytic, hyperchromic anemia has been produced in dogs by stricturing the small intestine and thus, according to one interpretation, producing changes in the intestinal wall which interfere with the absorption of the hemopoietic principle.⁴¹ Clinically, macrocytic anemia may appear in sprue, ileitis,⁴² and patients with intestinal strictures⁴³ or gastro-colic fistulae⁴⁴ where the absorption of the hemopoietic substance is undoubtedly interfered with, and in such patients parenteral therapy with the hemopoietic principle is of value in removing the anemia. (4) Sufficiently severe damage to the liver with resulting inade-

quate storage and elaboration of the hemopoietic principle should also produce a pernicious anemia-like blood-picture, if the physiological cycle outlined for the hemopoietic principle is correct. Experimentally, the repeated administration of large doses of carbon tetrachloride to dogs and rats with a consequent severe chronic liver damage and cirrhosis has led to the appearance of a macrocytic, hyperchromic anemia in some of the animals⁴⁵. The same result was obtained in a few dogs by gastrectomy followed by carbon tetrachloride administration⁴⁶. Clinically, there are many reports of macrocytic, hyperchromic anemia occurring in patients with cirrhosis of the liver^{47, 48, 49} and very probably some degree of macrocytosis occurs in nearly all patients with advanced diffuse liver disease^{50, 51}. Moreover, assay of the livers of patients with cirrhosis and a pernicious blood-picture has shown such livers to be deficient in the hemopoietic principle and the administration of the principle is effective in relieving the anemia in some of these patients.

We shall now consider data on two other points relative to the physiology of the hemopoietic principle. These involve its storage in sites other than the liver and its excretion. (1) Thus far the liver is the only proved site of detectable quantities of the hemopoietic principle. Dried, defatted hog stomach, duodenum, and probably jejunum, ileum, and colon are effective in the treatment of pernicious anemia when administered orally not because they contain the hemopoietic liver principle but because they contain its two precursors, the intrinsic and extrinsic factors. Salivary glands⁹ and muscle do not contain the liver principle. Neither do saliva,⁵² gastric juice,⁵³ or duodenal juice,⁵² although some workers have claimed that gastric juice does^{54, 55}. Kidney,⁵⁶ brain,⁵⁷ and pancreas have been shown to be effective in pernicious anemia when administered orally. Kidney is as effective as whole liver by mouth, whereas brain and pancreas are approximately one-third as effective. What the active materials in these organs are and what relation they have to the hemopoietic liver principle are not completely apparent at present. In the case of the kidney and brain, however, Dakin, Ungley, and West⁹ have presented strong evidence that the potent substance is not the hemopoietic liver principle, inasmuch as extracts of kidney and brain prepared by methods yielding potent parenteral liver extracts were ineffective parenterally in pernicious anemia. Recently we obtained similar results with kidney⁵⁸. (2) In view of the fact that the hemopoietic liver principle undoubtedly passes to the bone marrow via the blood stream, we examined normal human urine for the possible presence of the substance. First we found normal human urine to be reticulocytogenic for the pigeon similarly to liver extract⁵⁹. Other investigators have reported like findings using the rat⁶⁰ and guinea pig⁶¹. We then prepared an extract of urine by a method basically that employed in making liver extract and found the urinary extract to be reticulocytogenic for the pigeon. In the cruder chemical properties of solubility and relative heat-stability the reticulocytogenic urinary principle resembled the hemopoietic liver principle. However, in view of the non-specificity of the pigeon method of assay, the urinary

extract was then studied in pernicious anemia patients. Negative results in three patients showed definitely that the urine principle is not the hemopoietic liver principle.¹⁴ The hemopoietic principle, therefore, is not excreted as such in detectable quantities in the urine. Just what the relation of the reticulocyteogenic urine principle to the hemopoietic liver principle is cannot be stated at present, although we are inclined to consider the former a decomposition product of the latter.

In this brief discussion I have attempted to summarize for you certain features of our present knowledge of the chemistry, bioassay, physiology, and pathological physiology of the hemopoietic liver principle. As you have gathered, this knowledge in many respects is incomplete. However, as our knowledge of the principle increases, many of the present obscurities in the physiology of hematopoiesis and in the pathogenesis of certain of the blood dyscrasias will be swept away.

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THE HEMATOPOIETIC RESPONSE FOLLOWING ORAL ADMINISTRATION OF DESICCATED DUODENAL MUCOSA *

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THE fundamental work of Castle and his coworkers ^{1, 2, 3, 4} proving that a definite antianemic substance, "Intrinsic Factor," is produced in the wall of the stomach, at present seems to be established beyond a reasonable doubt. The theories developed by the author on the basis of this monumental discovery have, however, been questioned by a number of observers. Some of these objections, notably those of Greenspon,⁵ have had to do with the nature of the antianemic material and the method of its production in the stomach. A more serious discrepancy, however, exists in the theory that this vital material is developed only in the stomach and stored in various other structures of the body. It is the purpose of this paper to offer some facts to prove that this assumption is incorrect and that antianemic material is also produced in other portions of the gastrointestinal tract.

From a clinical point of view the fact that complete or at least extensive gastrectomy does not promptly produce the picture of a primary anemia should at once cast a reasonable doubt on the completeness of Castle's hypothesis. In 1933 Roeder⁶ collected from the literature the clinical records of 88 cases of complete removal of the stomach while Goldhamer⁷ in the same year following a similar search discovered only 23 cases of severe anemia following this operation. In Roeder's report reference was made to a case of A. W. Mayo Robson's living and in apparently good health 30 years following an almost complete gastric resection. Cases reported by Walters,⁸ Judd and Marshall,⁹ Clute and Mason,¹⁰ Morrison,¹¹ and others failed to exhibit any sign of pernicious anemia at intervals varying from several months to years following their operation. Poole and Foster's¹² case lived for three years following a complete gastrectomy without noticeable blood changes, then developed a pernicious anemia which responded well to appropriate treatment. These latter authors expressed the view that in any instance complete removal of the stomach would eventually lead to the development of an Addisonian type of anemia if the patient's post-operative life was sufficiently long.

In his 23 cases Goldhamer found only one individual in whom the anemia appeared as early as the fifth month, in the others it came on at intervals varying from one to 15 years. From this observation he concluded that the time element was an important factor in the development of the condition.

On the experimental side Ivy, Morgan, and Farrell¹³ reported in 1931, after a study extending over a period of seven years, that of 14 gastrectomized dogs, living for six months or longer following operation, three

* Received for publication February 25, 1937

developed a spontaneous anemia, and three were anemic only during pregnancy. The anemia observed was of secondary type and was responsive to treatment by iron. This work was confirmed by Mullen¹³, Dragstedt, and Bradley¹⁴ in 1933, and by Dragstedt, Bradley and Mead¹⁵ in 1935. Maisson and Ivy¹⁶ in 1933 reported similar observations on swine and suggested at this time that an intestinal factor might be the cause of their failure to produce a macrocytic hyperchromic blood picture. Judd and Marshall in their report on gastric resection stated that Mann had three dogs living over four years following gastrectomy, in good health and without anemia.

A study of the cases collected by Goldhamer and others is of especial interest in view of the results of the experimental physiologists, for it is quite apparent that at least some of the clinical records do not contain a sufficient amount of evidence to establish clearly a diagnosis of pernicious anemia and it is quite possible that some of these individuals suffered with the same hypochromic, iron requiring anemia which proved fatal in some of the experimental animals. It is further to be noted that a number of the dogs operated upon experimentally lived for years without developing a primary anemia. This would add some color to the views expressed by Poole, Foster and Goldhamer to the effect that time is an essential element in the development of the condition. While this premise is doubtless true then implied explanation cannot be accepted, for it is illogical to assume that the vital antianemic material is produced only in the stomach, and stored in the liver or other tissues in such inexhaustible quantities that its presence in effective amounts would be felt for months or even years after its source of renewed supply was completely abolished.

Further study of gastric secretion has also brought to light certain facts not adequately explained by Castle's postulates. This author in his investigation of two individuals suffering with typical Addisonian anemia but with apparently normal gastric juice found that the intrinsic factor was absent. In one individual with complete achylia but without anemia and in three persons suffering with anacidity and hypochromic anemia he found the material present. On the contrary Barnett¹⁷ in 1931 reported two cases, one of spure, and the other with a typical pernicious anemia, both of whom had normal gastric secretions containing a sufficient amount of intrinsic factor to produce a remission in an untreated case of the latter disease. In 1932 Barnett¹⁸ published a report concerning several cases of anacidity in which the intrinsic factor was missing but the individuals exhibited no signs of anemia. In 1935 Goldhamer, Isaacs, and Sturgis¹⁹ found that the gastric secretion of untreated cases of pernicious anemia contained appreciable quantities of intrinsic factor. They were able to demonstrate a definite relationship between the volume of gastric juice found in the stomach and the erythrocyte level in the usual case suffering with the disease. They also discovered that the average volume of gastric secretion was 20 c.c. per hour in the anemic individuals whereas normal persons produced 150 c.c. per hour. Their work would imply that a re-

duction in volume of gastric secretion would necessarily reduce the available supply of intrinsic gastric factor. Yet, Bloomfield and Pollard²⁰ found after a study of 45 cases of anacidity, extending over a period of one to seven years that not one of these individuals had developed a pernicious anemia. This group included two of the cases previously reported by Barnett in 1932 in whom the intrinsic factor was absent. At present these separate facts taken from the literature might be considered to be controversial in character and in the light of Greenspon's recent observations it is possible that failure to take into account peptic activity may have influenced the results obtained by various observers. There is suggested, however, from these experiments a possibility that intrinsic factor may be derived from other sources than the stomach. If the latter assumption is true then the cases first reported by Barnett were anemic because the unknown source of intrinsic factor was exhausted and the gastric supply was insufficient to handle the situation. In the cases of anacidity later reported by Barnett, Bloomfield, and Pollard anemia did not occur in the absence of intrinsic gastric factor for the reason that the unknown source adequately met the requirement for blood regeneration. The observations of Goldhamer, Isaacs, and Sturgis would suggest that if in the ordinary case of pernicious anemia the erythrocyte level paralleled the volume secretion of the stomach that in such usual cases the output of the second unknown source of supply must necessarily rise and fall with the volume production of the stomach. This would not only imply that the development of intrinsic factor is a quantitative reaction but would suggest some close physical relationship between the stomach and this as yet unrecognized source.

The idea that the gastrointestinal tract might provide a source of intrinsic factor production other than the stomach was discouraged by the original contribution of Castle who reported that this material was not demonstrable in normal human saliva or duodenal contents free from gastric juice. On the contrary Maison and Ivy in their work on swine suggested that an intestinal factor might enter into their failure to produce the hyperchromic blood picture. From the pathological view point Brown²¹ in a discussion of the pathology of pernicious anemia pointed out the frequent occurrence of lesions in the small intestine while the literature on the subject of tropical and non-tropical sprue has contained frequent reference to the presence of intestinal pathologic alterations.

From a clinical and experimental aspect the literature is not devoid of material suggesting the possibility of an intestinal factor in the production of hyperchromic anemia. In 1927 Seydewitz, Lehman, and Weichels²² reported that a pernicious anemia-like blood picture occurred in dogs after experimental stricture of the small intestine. In 1929 Little, Zervas, and Fressler²³ reported a clinical instance of pernicious anemia following lateral anastomosis and chronic small intestinal obstruction in man. During the same year Meulengracht²⁴ found 21 similar cases in the literature and reported another. In 1936 Hawksley and Meulengracht²⁵ reported still

another case and found that a total of 24 had made their way into the literature up to that time

At present Castle's postulate, to the effect that a lack of intestinal absorption of potent anti-anemic material is responsible for the development of certain cases of primary anemia, has been accepted as an explanation for the development of hyperchromic anemia in the above mentioned cases of intestinal stricture as well as in cases of idiopathic steatorrhea and sprue. It is, however, just as reasonable to assume that the blood picture in these conditions is due either partially or completely to a failure of the small intestine to produce in adequate amounts its share of the required intrinsic factor. If the latter assumption is correct then the frequent incidence of anacidity and disturbed gastric secretion in cases such as those cited above has a real significance for we must conclude then that primary anemia is essentially a condition produced by a definite quantitative loss of intrinsic factor production in both the stomach and intestine. Such a conclusion provides a more reasonable explanation for the results of experimental and clinical gastrectomy, for if the appearance of primary anemia is the result of the loss of a definite quantity of intrinsic factor produced in both the stomach and bowel the delayed development of this anemia must be due to gradually developing pathological changes in the intestinal mucosa and a destruction of its capacity to produce antianemic material. In this connection it must be emphasized that Castle's hypothesis assuming that all precursor substance arises in the stomach excludes any question of intestinal absorption in the cases of total gastrectomy for the reason that with intrinsic factor absent there should be nothing to absorb.

With this theoretical background it yet remains to offer some substantial proof that intrinsic factor can be and is developed in the intestinal tract. As was previously stated, Castle in 1928 found that antianemic activation of meat did not occur with duodenal section. In 1933 Kuehnau²⁶ carried out a number of feeding experiments which suggested that intrinsic factor was present in the duodenal juices. His work, however, was open to criticism for he employed a mixture of duodenal and gastric secretions. In 1935 Meulengracht²⁷ reported positive results in the treatment of primary anemia with duodenal mucosa, while Cheney²⁸ in 1936 discovered that liver extract incubated with duodenal mucosa produced an anti-anemic material of potency equal to or greater than that of the commercial product "Ex-tralin" developed in similar fashion by the incubation of liver with stomach mucosa.

The present work was undertaken in January 1935 and has been carried on continuously for a period of two years. During this interval a number of individuals suffering with pernicious anemia in relapse and various other anemic states have been given a preparation of desiccated duodenal mucosa with results which indicate the presence of a potent anti-anemic substance in the duodenum. The material used in this experimental work has been generously provided by the Research Division of the Eli Lilly Co., and has

been prepared by the usual methods of desiccation from the duodenal mucosa of swine. Each gram of the finished product has represented 4.5 grams of raw substance.

CASE REPORTS

Case 1 *Pernicious anemia in relapse*

History The patient, Geo C L, aged 66, carpenter, was seen on July 19, 1935, complaining of anemia, weakness, dyspnea on exertion, dull aching in the chest, palpitation of the heart, swelling of the feet and ankles, numbness and tingling in the hands and feet, dull aching in the limbs after a short walk, abdominal distress, slow stream and dribbling of urine. Some of these symptoms dated back to 1921 when a diagnosis of pernicious anemia had been made. During that year the anemia had been so severe that transfusion was done. Occasional relapses then occurred requiring transfusion until the advent of the liver diet.

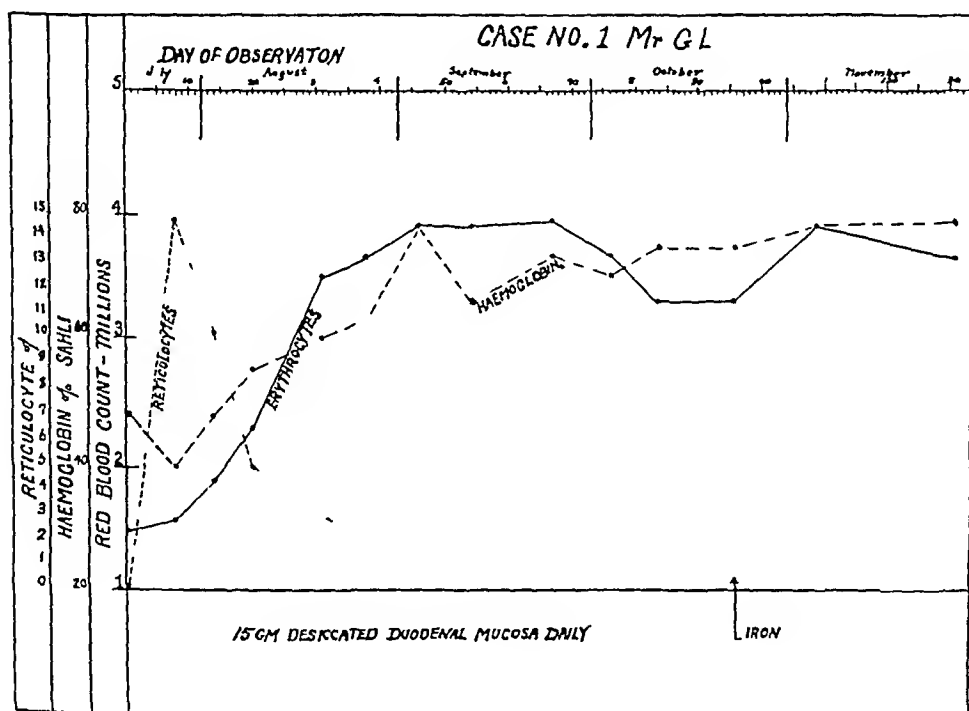


FIG 1

In July 1929 an office record indicates that he had been unable to work for a period of seven months because of weakness, numbness in the lower extremities, etc. Salient points of the examination at the time were: A lemon yellow pallor of the skin, red blood cells 2.62 millions, a systolic murmur at the cardiac apex, normal heart boundaries, blood pressure 120 mm of Hg systolic and 60 diastolic, liver edge just below the costal margin and a palpable spleen. Complete remission then occurred on Lilly's Liver Ext 343 in a dose of two vials three times daily. During the following years, owing to financial difficulties, the patient was able to maintain adequate treatment only at intervals and in consequence his erythrocyte level was subject to wide variations. On August 8, 1930, the red blood cells were 1.60 millions and the hemoglobin 35 per cent while on February 21, 1933, the red blood cells were 4.84

millions and the hemoglobin 82 per cent. Response to proper therapy during this interval, however, was always satisfactory. From February 21, 1933 on, a physician was not consulted until he presented himself for treatment on July 19, 1935 with the symptoms outlined above, most of which had been present for a considerable period of time.

Physical Examination. The patient was a moderately thin white male. Pulse 72. Temperature 98.6° F. Pupillary reactions were normal. Pyorrhea and recession of the gingivae were noted about the remaining teeth. The tongue was slightly coated but the papillae were still present and there was no evidence of glossitis. Mucous membranes were pale. The radial arteries were thickened. The heart was slightly wide at the base. The heart sounds were somewhat muffled, a roughness of the first sound was heard in the aortic area, and a systolic murmur, not transmitted, was present at the apex. The lungs were emphysematous and subcrepitant râles were heard on inspiration particularly over the bases. The liver edge was three fingers-breadth below the costal margin. The spleen was not palpable. The feet were cold and clammy and pulsation in the dorsalis pedis arteries could not be definitely palpated. Vibratory sense was somewhat questionable. Neurological examination otherwise was negative. The prostate was atrophic, its secretion contained considerable pus. Dorsal kyphosis with moderate limitation in movements of the spine was noted.

Laboratory Examinations. Upon roentgen-ray investigation the thoracic aorta was found to be slightly dilated and its shadow increased in density. The excursion of the diaphragm was limited and some infiltration was noted along the lower bronchi. The gastrointestinal tract was negative except for moderate ptosis.

The hemoglobin was 48 per cent (Sahli). The red blood cell count was 1.45 million. Volume index was 1.2. Reticulocytes were absent. Poikilocytosis and anisocytosis were noted as well as a very definite macrocytosis. The white blood cell count was 9,700 and upon differential count there were 40 per cent lymphocytes, 3 per cent monocytes, 4 per cent juvenile forms, 10 per cent rod forms and 51 per cent segmented cells. Of the latter, 34 per cent contained three or more divisions of the nucleus. The blood Wassermann test was negative. The stomach contents contained no free acid after histamine. Blood calcium was 9.5 mg. and phosphorus 3.2 mg. per 100 cc. of blood. The bromsulphalein liver function test, at 5 minutes, showed 40 per cent retention of dye, at 15 minutes 25 per cent, and at 30 minutes none. Urine was negative.

Treatment and Progress. On July 19, 1935, the patient was placed on 15 gm. of desiccated duodenal mucosa, representing 72 gm. of raw material daily. This treatment was continued without interruption and with no other medication until September 11, 1935, a total of 54 days. The reticulocyte count increased from zero to a peak level of 14.8 per cent on the eighth day. The erythrocyte count changed from 1.45 million on July 19 to 3.9 million on September 3, a total of 46 days, and an average gain of 375,000 cells per week. Hemoglobin rose from a low point of 40 per cent to 78 per cent on September 3. Because of slight edema of the feet and ankles, a slight dyspnea on exertion, and some enlargement of the liver the patient was given digitalis in a dose of 4½ grs. of powdered leaf daily beginning September 11. This treatment has been continued at intervals. On October 23, 1935, a moderate dose of iron was prescribed. In December 1935 an investigation of the bladder for residual urine was negative. During the early months of 1936 the patient had an acute respiratory infection and some trouble with hemorrhoids requiring treatment. On March 30, 1936, the red blood cells were 4 million and hemoglobin 90 per cent. During the months of April, May, and most of June the patient did not return for observation and received no treatment. On June 27, 1936, the red blood cell count had dropped to 2.9 million and the hemoglobin to 64 per cent. On December 9, 1936, on treatment the red blood cell count was 4.4 million and the hemoglobin 87 per cent.

The total period of observation in this case has been 18 months. During this interval the erythrocyte count has been maintained at a satisfactory level on relatively small amounts of desiccated duodenal mucosa and has dropped very definitely on one occasion when the patient failed to take this material over a considerable period of time. General health has been very much improved although some symptoms due to arteriosclerosis persist and are troublesome.

Case 2 *Pernicious anemia in relapse*

History The patient, Mrs. M. H., aged 47, was first seen on April 1, 1936. The major complaints at the time consisted of a feeling of fatigue and weakness, and a numbness in the hands and feet. The latter symptom was so severe that the patient lacked definite control of her extremities. She could not walk in the dark without assistance, and she frequently dropped dishes and other objects from her hands. She had experienced a soreness of her tongue at its tip and edges at intervals for three years. She suffered with anorexia, nausea, salivation, flatulence and constipation. She complained of a low backache, nervousness, and leukorrhea. The development of these symptoms had occurred over a period of months to years. The menopause had occurred three years previously. History in all other respects was essentially negative.

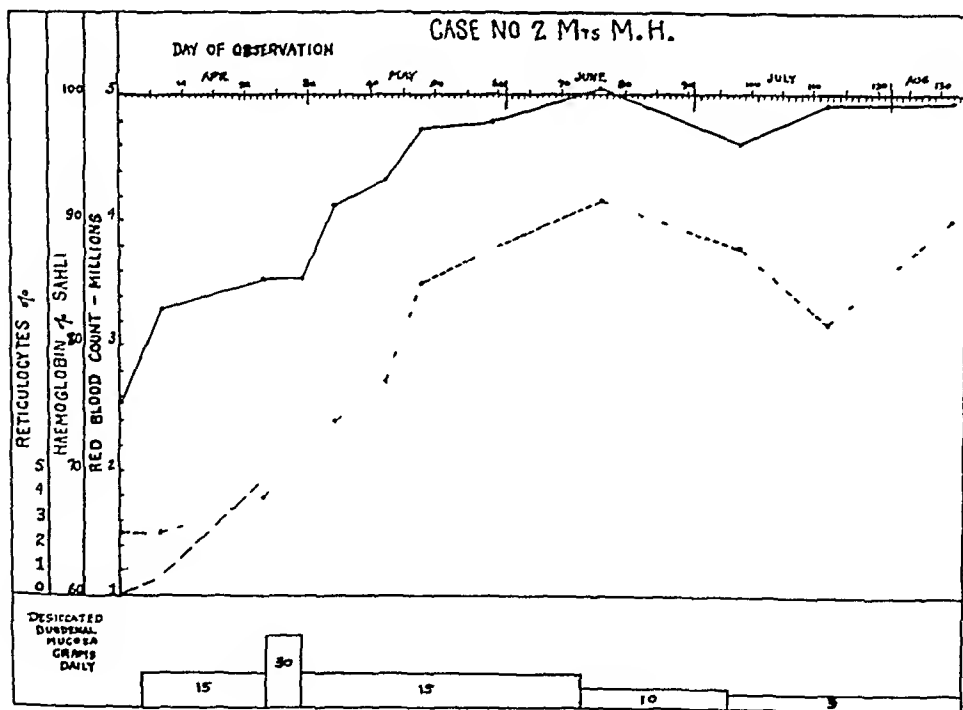


FIG 2

Physical Findings Upon physical examination temperature was 99.5° F, pulse 76, and weight 10 pounds over optimum normal. The skin had a distinctly lemon yellow color. The mucous membranes were pale, and the sclerae pearly white. The tonsils were chronically inflamed. Considerable pyorrhea and gum recession were noted. The papillae of the tongue were not atrophic but patchy reddened areas

occurred along its edges. A cystic type of goiter was present of moderate size. The heart and lungs were negative. Blood pressure was 108 systolic and 74 diastolic. The abdomen was negative except for the presence of a spastic palpable sigmoid and moderate tenderness in both lower quadrants. Pelvic examination was negative. The knee jerks were sluggish. Plantar reflexes were normal. Epicritic sensibility was diminished and vibratory sense was absent. Romberg's sign was questionable. Hypertrophic changes were noted in the terminal interphalangeal joints.

Laboratory Data The laboratory data were as follows: Erythrocytes 2.5 million, hemoglobin (Sahli) 65 per cent, Volume index 1.2, Color index 1.3, White blood cells 3700. A definite macrocytosis was present with anisocytosis and poikilocytosis. The differential count was lymphocytes 64 per cent, monocytes 2 per cent, stab forms 10 per cent, segmented cells 24 per cent. No free acid was present in the stomach contents after histamine. The stool contained no blood, ova, or parasites. The blood Wassermann was negative. Blood calcium was 11.5 mg per cent. Basal metabolic rate was plus 11. Urine was negative.

Treatment and Progress A diagnosis of pernicious anemia was made and treatment was started on April 4, 1936. The patient was given desiccated duodenal mucosa in a dose of 15 gm daily from April 4 to April 24. During this interval a gain of 940,000 cells occurred or an average weekly increase of 329,000. On April 24 the dose was increased to 30 gm daily for a few days followed by a daily administration of 15 gm daily until June 15. The blood picture had returned to practically a normal condition on May 18, a total of 44 days. On June 15 the dose was reduced to 10 gm daily. The average quantity consumed daily between the dates of July 6 to September 23, 1936, was 9 gm. No other therapy was advised with the exception of rest during the early phases of treatment and dental therapy which was started on May 28.

Upon the date when treatment was instituted the patient was hardly able to be up and about. Gastrointestinal complaints had disappeared by April 24 and the blood counts had returned to normal by May 28. The patient at this time was doing all of her own work. By July 21 she had very little complaint with reference to paresthesias and was scrubbing, washing, ironing and doing a large amount of hard work each day. The patient was last seen on January 18, 1937, at which time in spite of rather small dosage her erythrocytes were 4.4 million and hemoglobin 97 per cent. She had no complaints at this time.

Case 3 Pernicious anemia in relapse

History The patient, Mrs. W. C., aged 81, entered the Lincoln General Hospital on March 19, 1936, complaining of nocturia, diurnal frequency, and pain in the upper right quadrant. These symptoms had confined the patient to her bed for two weeks. In addition she had suffered with weakness and fatigue for six months, anorexia for four months, numbness in the hands for four months, slight dyspnea for years, and moderate edema of the feet and ankles. Coincident with urinary symptoms the patient had also suffered with pain and distress in the right flank and right upper abdomen.

Examination The patient was well nourished. Temperature 98° F, pulse 84. The skin had a definite lemon yellow color and the sclerae were pearly white. The tongue was smooth and areas of redness were found along the edges. The heart boundaries were normal. The peripheral arteries were not sclerosed. A systolic murmur was heard at the cardiac apex. A rather marked tenderness and rigidity were noted in the upper right quadrant and right flank. Vaginal examination was negative. A slight pitting edema was noted in the ankles. The knee jerks were sluggish. Vibratory sense was lost in the lower extremities. Plantar reflexes were normal.

Laboratory Data The urine on March 19, 1936, contained considerable pus. The erythrocytes were 1.36 million and the hemoglobin was 38 per cent (Sahli). Volume index was 1.4. Reticulocyte estimation was 0.8 per cent. Macrocytosis, anisocytosis,

poikilocytosis, and polychromatophilia were present. The differential was lymphocytes 50 per cent, monocytes 25 per cent, metamyelocytes 15 per cent, eosinophiles 1 per cent, basophiles 05 per cent, segmented forms 44 per cent, stab forms 05 per cent. On March 21, the stomach contents contained no free acid. On March 24, a urine culture was positive for *Escherichia coli*. Intravenous pyelogram done on April 7 showed a normal kidney function with normal pelvis and ureters.

Treatment and Progress. Thirty grams of desiccated duodenal mucosa were given daily beginning on March 20, 1936, and continuing until the patient left the hospital on April 12. During this interval the erythrocytes increased from 136 million on March 19, 1936, to 159 million in four days, to 168 million in seven days, to 197 million in 13 days and 245 million in 20 days. Reticulocytes multiplied from 08 per cent on March 19 to 96 per cent 10 days later. Daily counts were not made and the

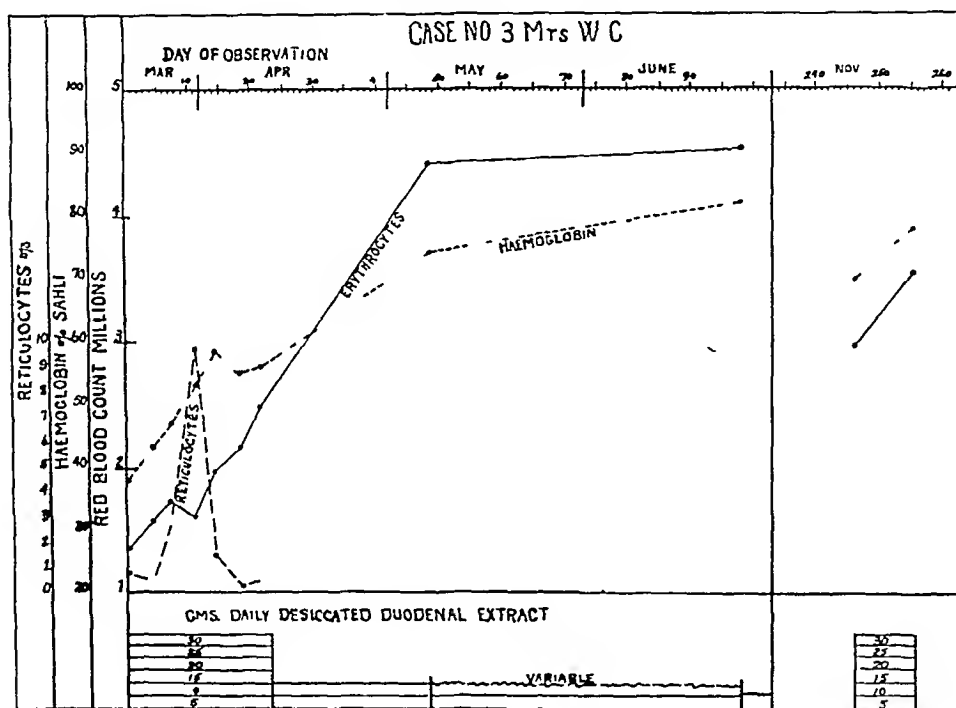


FIG 3

peak probably occurred prior to this day. Hemoglobin increased from 38 per cent to 56 per cent on April 9. A diagnosis of a right infected hydronephrosis was made which was thought in turn to be possibly due to a cord bladder. Treatment for this condition consisted of bed rest, urinary antiseptics, nitrohydrochloric acid, bladder catheterization and lavage. The infection cleared up promptly.

On the twenty-third day the patient was discharged from the hospital in very good condition with a supply of desiccated mucosa and a request to report at frequent intervals. Instructions were given to take 15 gm of the material daily but the dose was reduced and the patient did not return until May 6. On this, her forty-seventh day of treatment, the erythrocytes were 44 million and the hemoglobin was 74 per cent. The increase of red blood cells for the 47 day period amounted to 305 million or an average per week of 450,000 cells. At this time the patient was not only doing some housework but was also spending some time in her garden.

In spite of a warning the patient continued to be careless in her attitude toward the use of antianemic material. Between the dates of June 19 and September 11, she

consumed a total of 540 gm on a daily average of 6 gm. After September 11 she had no treatment until she finally returned on November 20, 1936. At this time she had no particular complaints. She had suffered with no recurrent abdominal distress or urinary symptoms and her urine contained no pus. Her erythrocytes, however, had fallen to 2.9 million and the hemoglobin was 70 per cent. She was again given 30 gm daily and nine days later the erythrocytes were 3.57 million and the hemoglobin 78 per cent. Subsequent changes in the erythrocyte count are unknown for the patient left the city for the winter.

Case 4 Pernicious anemia with combined sclerosis of the spinal cord

History The patient, Mrs. F. W. J., aged 64, housewife, first presented herself for examination on January 24, 1935, with the outstanding symptom of abdominal distress. She stated that this trouble had been present for years and was accompanied by a severe constipation requiring constant catharsis, flatulence usually aggravated by cabbage, raw apples, etc., occasional passage of light colored stools, and pain of moderate severity usually felt in the lower abdomen but occasionally experienced above. She had been troubled with hemorrhoids, and bright red blood had appeared in her stools frequently over a period of 20 years. In addition she complained of weakness, nervousness, a numbness in the lower extremities present for the preceding five months, and a frequent soreness of the mouth which she described as canker sores. The latter had occurred over a period of at least four years. For years she had also been troubled by a loss of the sense of smell. This symptom had developed after a severe head cold. In other respects the history was essentially negative.

Physical Examination The patient was 35 pounds under her normal weight. Temperature was 98° F, pulse 84. The examination of the head and neck was negative, excepting for the presence of several questionable teeth. Blood pressure was 164 systolic, and 96 diastolic. Peripheral vessels were normal. The heart was of normal size but a slight roughness of the first and a reduplication of the second tone were heard at the apex. The lungs were negative. A tenderness and a sense of resistance were noted in the upper right quadrant and the sigmoid was tender, spastic and palpable. The liver edge was slightly below the costal margin. The spleen was not palpated. Vaginal examination was negative. Upon inspection a number of inflamed hemorrhoids were noted. The knee jerks were sluggish. Circulation in the lower extremities was normal.

Laboratory Data (First admission) A non-functioning gall-bladder with gastroparesis, cecal stasis, and a slowing of the gradient through the large intestine was found on roentgen-ray examination. No free acid was present in the stomach contents either before or after histamine. The urine was negative. Icterus index was 10. Blood calcium was 8 mg and phosphorus 3.2 mg per 100 cc of blood. Hemoglobin was 85 per cent. Red blood cells were 3,880,000, and white blood cells 4700. Upon differential count the cells were classified as follows: Lymphocytes 60 per cent, monocytes 2 per cent, juvenile forms 6 per cent, stab forms 6 per cent, and segmented cells 26 per cent. Volume index was not done. A slight poikilocytosis was noted. Blood Wassermann test was negative. The stool contained neither parasites nor blood but was thin as a result of catharsis.

Initial Treatment Following this examination the patient was admitted to the Bryan Memorial Hospital and operated on February 18, 1935. The gall-bladder was found to be thick-walled, gray, and adherent to the duodenum. The appendix was retrocecal and adherent to the terminal ileum. Both were removed as well as three large, protruding internal hemorrhoids. The patient was discharged from the hospital on March 3, 1935, with no complaints and her strength rapidly improving.

History and Examination (Second hospital admission) The patient reentered the hospital on May 23, 1935, with the statement that for one month after being discharged on March 3 she had noted a very definite improvement in strength and felt no paresthesias. At the end of this time, however, there gradually developed

a marked numbness with peculiar sensations of burning, and tingling in the hands and limbs, difficulty in walking, weakness, and an abdominal distress arising chiefly from constipation

Upon examination the patient was undernourished, and unable to support her weight on her limbs. The tongue was very smooth. The abdomen was distended and the wall was thin. The knee jerks and tendo-achilles jerks were absent. The plantar reflexes were very sluggish. Both epicritic and vibratory senses were absent. Muscle strength in the limbs was fair but the patient was unable to stand or walk because of ataxia of the lower limbs. Finer movements of fingers and hands were also affected. Muscle sense in the limbs was impaired. On May 27 the erythrocyte count was 3.2 million and the hemoglobin 80 per cent. No reticulocytes were present. Volume index was 1.18. White blood cells, 5000. Poikilocytosis and anisocytosis were noted. Differential count was: Neutrophile rods 3 per cent, segmented cells 49 per cent, lymphocytes 46 per cent, and monocytes 2 per cent.

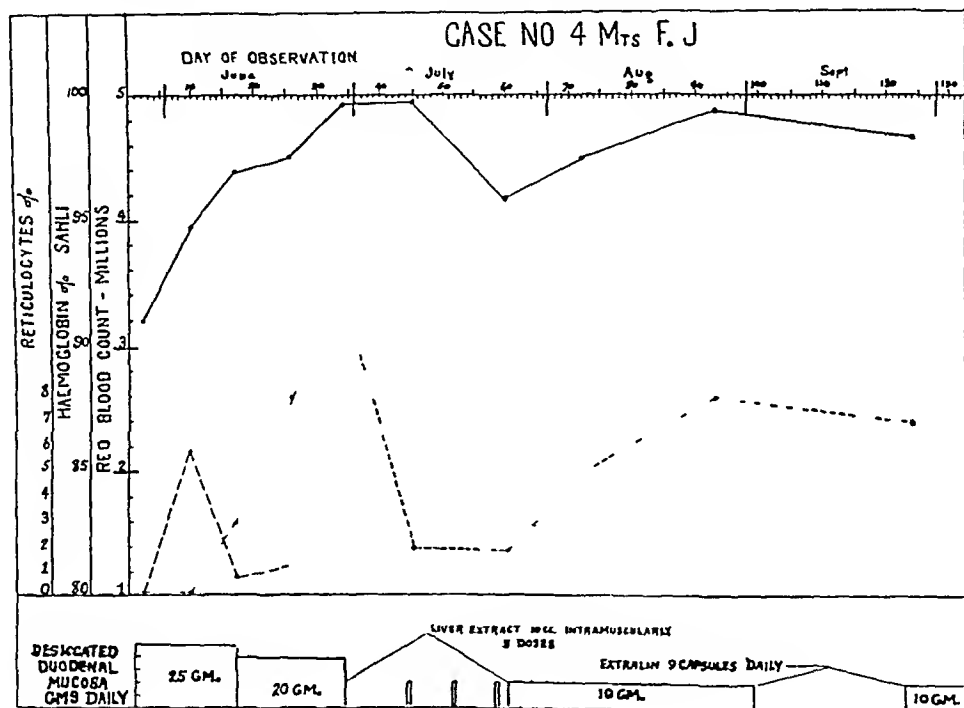


FIG 4

Treatment and Progress. On May 26 the patient was started on desiccated duodenal mucosa in a daily dose of 25 gm. After 17 days this dose was reduced to 20 gm daily and continued for 17 days. At the end of 34 days the patient was tried at intervals on liver extract intramuscularly, extralin and later ventriculin. On each occasion, however, after a few days a definite loss of strength and an increase of symptoms were noted. A maintenance dose of 10 gm of duodenal mucosa was started at the end of 60 days and has been continued with a few interruptions until the present time.

A definite improvement in symptoms was recognized as early as 12 days after the beginning of treatment. At the end of 32 days the patient was able to walk about her home and in her garden with the assistance of a cane. At the end of six months very little or no trace of the former ataxia could be noted. Knee jerks were sluggish but present. Epicritic sensibility had returned but vibratory sense was very

uncertain or absent. A very definite relief from digestive disturbances particularly constipation was also observed on duodenal mucosa while the latter symptom was troublesome while taking ventriculin or liver.

On June 28, 1935 thirty-four days after treatment was started, the erythrocytes were 488 million and the hemoglobin 92 per cent. Since this time normal erythrocyte and hemoglobin levels have been obtained with the exception of moderate decreases occurring especially when treatment with other antianemic substances was utilized in probably inadequate dosage. A definite reticulocyte response occurred with a peak level of 59 per cent at the end of 10 days of treatment on desiccated duodenal mucosa.

Between the dates June 4 and October 2 a total of 120 days the patient was given a daily ration of approximately 12 gm daily. During this interval she maintained a normal erythrocyte count. During the following four months the patient's supply was curtailed and she was advised to use other anti-anemic substances. Whenever a supply was given to the patient during this interval she was required to appear for observation. This entailed a 70 mile auto trip which the patient on all occasions was eager to make for the reason that subjectively she repeatedly noted that she felt better and was stronger when taking desiccated duodenal mucosa.

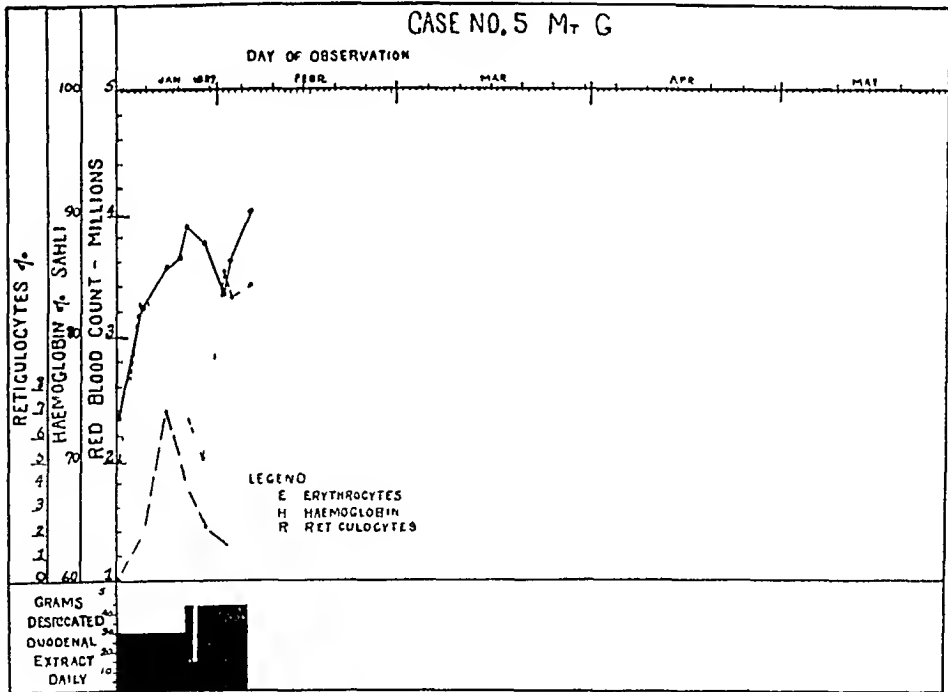


FIG 5

Case 5 Pernicious anemia with combined sclerosis of cord

History The patient M+ G, aged 53, store clerk by occupation, was first examined on January 14, 1937. He came in complaining of a stiffness in his legs and a feeling of tightness and pressure in the abdomen which he stated had been gradually developing over a period of months. He further complained of a wooden sensation in his hands and feet, a difficulty in walking in the dark, a sexual impotence of 6 to 7 months' standing, a lack of strength, constipation, flatulence, and abdominal distress. He had been unable to work for a period of six months. Past history was negative with the exception of a history of albuminuria 10 years previously.

Examination: Upon physical examination the weight was normal (178 pounds) Temperature was 99.2° F pulse 64. A definite pallor was present. Sclerae were pearly white. The edges of the tongue were bald. The cardiovascular system was negative. Blood pressure was 140 systolic and 76 diastolic. The liver and spleen were not palpable. The abdomen was slightly tympanitic but otherwise negative. The testicles were atrophic. Neurological investigation revealed the presence of a positive Romberg, normal pupillary reactions, exaggerated knee jerks, and tendo-achilles jerks with normal plantar reflexes. Muscle sense was disturbed and a moderate loss of epicritic sensibility was noted in the lower limbs.

Laboratory Data: The laboratory data were as follows: Erythrocytes 2.2 million hemoglobin (Sahli) 70 per cent, white blood cells 5500. Reticulocytes were absent. Anisocytosis, poikilocytosis, and macrocytosis were present. Volume index was 1.1+. Differential count: Lymphocytes 28 per cent, stab forms 12 per cent, segmented neutrophils 58 per cent, juvenile forms 2 per cent. No free acid was present in the stomach after histamine. Blood Wassermann was negative.

Treatment and Progress: On January 15, 1937, the patient was started on 30 gm of desiccated duodenal mucosa daily. This dose was increased to 45 gm daily on January 26, and with one interruption was continued until February 5, a total of 20 days. During this interval the red blood cells increased to 4 million, an average weekly increase of 600,000 cells. The reticulocyte count was probably not taken at its peak but was found at 7 per cent on the ninth day. During this interval the patient was not permitted to walk, but strength and color improved. Constipation was relieved as well as abdominal distress. Neurological changes in the lower extremities remained unchanged.

The red blood count on March 11, 1937, was 5,190,000, hemoglobin was 110 per cent and since this time the hemoglobin has never been below 100 per cent and the red count never less than 5,000,000 up to the present, June 23, 1937. Further, the patient is now able to walk without support of any kind for a considerable distance without tiring. There remains only a very slight feeling of stiffness in the limbs.

Case 6 Non-tropical spiro

History: The patient, Mrs. C. P., aged 32, was first seen on April 24, 1934, complaining of diarrhea, gas, belching, bloating, cramping and abdominal distress, sore mouth and tongue, nervousness, fatigue, and heart burn.

She stated that her illness really started very insidiously while she was engaged in training for the vocation of nursing between the years of 1924 and 1927. During this interval her diet was extremely poor in general quality, contained very little meat, and consisted principally of starchy foods. The dietary habit so established was continued after graduation to a considerable degree and particularly so after a diagnosis of peptic ulcer was made in 1929.

Approximately five years previously the patient had rather suddenly developed a diarrhea associated with fever, and distress in the upper abdomen. She was suspected of having tuberculosis and was placed in bed for a period of six weeks. Fever subsided in six weeks but watery stools continued for six months. Since that time diarrhea had recurred two or three times each year and continued for intervals of six weeks to three months. At the height of this trouble as many as 10 to 12 stools were passed daily. In the intervals movements were normal. During the attacks of diarrhea the patient noticed a marked tendency for movements to occur between 4 and 5 a.m. causing a disturbance of rest and sleep. More trouble had been experienced in summer than during winter months.

Flatus, bloating and passage of large quantities of gas occurred at the onset and had continued to cause trouble. Rather marked distress was felt in the upper abdomen particularly in the first attacks. Tenesmus and pain accompanied this difficulty. In subsequent attacks these symptoms were not so severe. Heart burn had been present much of the time during the five year interval. Dilute hydrochloric acid

was tried for this trouble but it irritated the mouth and aggravated the symptom. In each attack of diarrhea a swelling of the lips and mucous membranes of the mouth had developed. There were also sores on the tongue which the patient described as not being the usual canker sore. Nausea and vomiting had occurred only at rare intervals and then only when some intercurrent infection was present.

Nervousness had been marked throughout the course of the illness. Limited strength and fatigue were early and persistent symptoms. The patient's strength was not sufficient to permit her to do her usual work and she was required to rest for at least two hours each afternoon. She had noted that fatigue seemed to aggravate her other troubles.

Upon further questioning it was found that the patient had never suffered with numbness, paresthesias, joint pains or muscle cramps. Insomnia had been experienced only to a slight degree.

Menses occurred at irregular intervals varying from 28 to 42 days. The flow was scanty and continued for five days. Pregnancy with death of one twin on delivery had occurred some two years previously. This had been followed by a severe attack of pyelitis. The history in other respects was negative.

Examination (April 24, 1934) The patient's weight was 87½ pounds. Height 60½ inches. Optimum weight 121 pounds. Temperature was 98.8° F, pulse 62. Blood pressure was 112 systolic and 86 diastolic. Patient's color was naturally dark and an undue pigmentation of the face and arms could not be definitely determined. Head and neck were entirely negative except for a few palpable glands in the posterior triangles of the neck. The heart and lungs were negative. The abdomen was distended. The wall was thin, flabby, but symmetrical. Loops of bowel could be noted through the abdominal wall. There was no tenderness or other findings. No edema of the feet and ankles was present. A slight grating was noted in the left shoulder. Vaginal examination was negative. Proctoscopic examination revealed some muscular spasm in the pelvic colon and a slight irritation of the mucosa but no hemorrhoids and no cryptitis.

Laboratory Data Upon radiological examination some calcification was noted in the right hilus with increased lung markings extending downward and outward from this area. The stomach was hyperperistaltic but otherwise negative. Barium lagged in the second and third portions of the duodenum and the normal markings of the *valvulae conniventes* were not present for some distance in the jejunum.

A number of stools examined were found to have the same general characteristics. They were of grayish color, soft consistency, foul odor, and contained a large amount of fat. Starch, muscle fibers, ova, parasites, pus, blood and mucus were absent. Occult blood was noted in traces.

The erythrocyte level on April 24, 1934, was 3.9 million, the hemoglobin was 74 per cent. Erythrocytes had a poor color, and were somewhat irregular in size. A definite macrocytosis was present. The white blood cell count was 4,200 and the differential count showed lymphocytes 46 per cent, juvenile forms 4 per cent, stab forms 4 per cent, and segmented cells 46 per cent. Definite deviation to the right was noted. The blood Wassermann test was negative. Blood calcium was 7 mg. per 100 c.c. of blood. Blood urea was 20 mg. per 100 c.c. On a fasting stomach, blood sugar was 89 mg. and rose to a maximum of 98 mg. in one hour after glucose ingestion. Stool culture on ordinary media was negative but was positive for a fungus on Sabouraud's media. Urine diastase was negative. Stomach acidity was within normal limits.

Treatment and Progress The patient was placed on a practically fat free, high protein, and low carbohydrate diet. Later medication was given at intervals consisting of viosterol 10 ggt. three times daily, 2 c.c. of liver extract intramuscularly three times weekly, calcium lactate 10 gr. three times daily and still later ventriculin with

iron On January 29, 1935, after nine months of the above treatment, the patient summarized her condition as very definitely improved but not satisfactory

On January 30, 1935, the patient was placed on desiccated duodenal extract in a dose of 10 gm daily This was soon increased to 15 gm and has been continued with a very few short interruptions for two years During this interval the patient has had no other medication but has continued to observe the dietary program previously mentioned

On January 29, 1935, the blood picture was as follows Erythrocytes 4 million Definite macrocytosis present Reticulocytes 0.5 per cent, white blood cells 3,900 Differential count Juvenile forms 10 per cent, monocytes 6 per cent, lymphocytes 40 per cent, rod forms 14 per cent, segmented cells 28 per cent, eosinophiles 2 per cent On February 15, 1935, the erythrocytes were 5 million This very definite improvement in the blood picture has been constantly maintained since that date In the same 16 day interval the blood calcium and phosphorus also increased to normal levels and have been maintained with few interruptions The stools have been free from an excess of fat except on a few occasions, particularly when the patient tried to take too much fat in her diet On such occasions the stools have been loose and the blood calcium and phosphorus have also been found at lower levels The symptoms of flatulence, abdominal distress, sore mouth and tongue, lack of strength, insomnia, nervousness, abnormal stools have not occurred for 18 months The last difficulty occurred for a short period in June 1935 The patient has made a slow but steady gain in weight and her appetite is very good She has been able to do her work without fatigue and is in better health than she has enjoyed for years The patient was last seen on January 18, 1937, at which time she had no complaints Her erythrocyte count was 5 million, and hemoglobin was 109 per cent

Case 7 Non-tropical sprue

History The patient, Mrs J V, aged 48, was seen on February 7, 1935, complaining of anemia, intermittent diarrhea of 32 years' duration, a burning sensation in the mouth and rectum, abdominal distress, flatulence, undernutrition, and insomnia Upon examination undernutrition was noted Face and neck were quite bronzed The tongue was smooth The abdomen was tympanitic Some soreness and restriction of motion were noted in the left shoulder and hypertrophic changes were found in the terminal interphalangeal joints The stools contained no parasites but were mushy and contained an excess of fat The stomach contents were without free HCl after histamine stimulation Blood calcium was 7 mg and phosphorus 3.3 mg per 100 c c of blood Erythrocytes were 3.8 million, hemoglobin 83 per cent (Sahli) Volume index was 1.09 White blood cells 6,150 Differential count Rod forms 10 per cent, segmented cells 37 per cent, eosinophiles 4 per cent, basophiles 0, lymphocytes 42 per cent, monocytes 6 per cent, juv forms 1 per cent Macrocytosis, anisocytosis, poikilocytosis, and polychromatophilia were present

The patient was given a diet restricted in fat, dilute HCl, and 15 gm of desiccated duodenal mucosa daily On this regime she felt an improvement as early as the fourth day On February 22, the fifteenth day of treatment, the erythrocytes were 4.9 million and the hemoglobin 85 per cent The patient continued to do nicely for a period of three months At the end of that time further effort to continue observations on the results of treatment were discontinued for the reason that the patient lived in a distant city and could not report

DISCUSSION OF CASES

A critical analysis of the case histories presented indicates that the therapeutic effect of desiccated duodenal mucosa is similar to, or even better than, the results obtained from the use of desiccated stomach preparations The dosage employed in the cases reported was in each instance much less

than the quantities recommended for the latter material yet the erythrocyte response amounted in all cases to 300,000 cells or more per week, whereas an increase of 100,000 cells per week is considered to be satisfactory with stomach preparations.

The reticulocyte response unfortunately could not be determined with sufficient frequency to absolutely establish the relative potency of the material employed and in no instance is there any assurance that the height of the reaction was recorded. In Case 1, however, an increase of 14.8 per cent occurred on the eighth day after administration of 15 gm. of desiccated duodenal extract. The initial erythrocyte count in this instance was 1.45 million. According to Bethell and Goldhamer's table for a similar initial count the height of the reticulocyte response after feeding 40 gm. of desiccated stomach mucosa daily should be 29 per cent. With less than half the dose, therefore half the expected increase of reticulocytes was obtained. In Case 4 with an initial count of 3.2 million the reticulocyte response at its height should be 3.1 per cent, after taking 40 gm. of stomach mucosa daily. In this case with 25 gm. of desiccated duodenal mucosa an increase to 5.9 per cent was found on the tenth day. The clinical improvement in every instance was satisfactory and normal erythrocyte levels were maintained in at least three cases for a sufficient time to exclude the possibility of spontaneous remission having occurred.

A study of six cases of gastrointestinal difficulty associated with anemia, diarrhea, and colitis has indicated that, in addition to its antianemic properties, the preparation has qualities which may be of considerable therapeutic value in the treatment of such conditions. The improvement noted may be due to the presence of intestinal ferments.

COMMENT

The above work it must be remembered deals with a material derived from the duodenal mucosa of swine. This cannot be considered in any way as direct proof that a similar antianemic substance may be found in the intestinal mucosa of man. A careful review of the literature, however, would indicate that such an assumption should be made. Castle's work with duodenal secretion should be carried further to show the effect on a primary anemia of the administration of human duodenal mucosa, or the response to the product of the interreaction between human duodenal mucosa and beef extract. It is possible that some chemical reaction or ferment activity may change or modify duodenal secretion so that in Castle's experiment negative results are obtained.

CONCLUSIONS

1. A study of the literature indicates a weakness in Castle's assumption that *intrinsic factor* is produced only in the stomach.
2. Many of the uncertainties arising from Castle's hypothesis may be

reasonably dispelled by the assumption that *intrinsic factor* is produced quantitatively in both the stomach and bowel

3 Proof that potent antianemic material is found in the duodenal mucosa of swine is presented

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THE ORIGIN OF PAROXYSMAL TACHYCARDIAS AS DETERMINED BY THE ESOPHAGEAL ELECTROGRAM *

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IN order to differentiate clearly the various types of sudden increase in the cardiac rate electrocardiographic records are necessary. In view of the fundamental differences in the method of treatment employed in these instances of paroxysmal tachycardia an exact diagnosis is desirable. In many instances the auricular complexes are not clearly discernible in the three conventional leads, and the cardiac rhythm cannot be determined with certainty. For example, the difficulty in distinguishing paroxysmal auricular tachycardia and auricular flutter with one to one response is especially great.

The esophageal electrogram is of practical aid in the diagnosis of abnormalities of the auricular rhythm as the P-waves are large and clearly defined in these records. The method described by W. Hurst Brown¹ has been used in the study of the cardiac arrhythmias presented in this report. If care is taken to anesthetize thoroughly the pharynx with a 5 per cent solution of butyn no difficulty will be experienced in passing the electrode. In ambulatory patients the position of the esophageal electrode is checked by fluoroscopy. With the patient placed in the right anterior oblique position the cardiac outline is traced on a piece of tissue paper held in front of the fluoroscopic screen. The exact position of the electrode in relation to the posterior surface of the heart can be accurately recorded in terms of depth in centimeters from the teeth upon this outline. After this procedure has been carried out the electrode can be placed at the various points without fluoroscopic control. By averaging the results obtained by fluoroscopic control Brown found that the multiplication of the measurement in centimeters from the thyroid cartilage to the tip of the ensiform process by 1.33 always indicated the depth in centimeters from the teeth necessary to bring the electrode behind the left auricle. This method is used when fluoroscopy cannot be performed.

Three cases of paroxysmal supraventricular tachycardia, one case of paroxysmal ventricular tachycardia, and one of indeterminate origin have been studied in this manner. Before presenting them a brief description of the form of the normal esophageal record seems advisable.

When the esophageal electrode lies behind the left auricle the main characteristic of the P-wave is a sharp upstroke indicating electro-negativity of the small area just beneath the electrode. The onset of auricular activity is usually represented by a small upright or "extrinsic" deflection repre-

* Received for publication February 12 1937

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sending the summation of activation of points in the auricle distant from the electrode. The downward deflection just before the sharp upstroke or intrinsic wave indicates the rapid approach of the excitation wave to the cardiac muscle lying in closest approximation to the electrode. Whenever the electrode is not lying over the auricle the sharp upstroke or intrinsic deflection will be absent. Figure 7B shows the form of the esophageal electrogram at various levels. There is no need to comment in detail on the form of the ventricular complexes in these records.

PAROXYSMAL SUPRAVENTRICULAR TACHYCARDIA

Case 1 M. B., a 63 year old white woman, had had an attack of palpitation followed by vertigo and loss of consciousness at the age of 18. She had had several similar attacks each year since that time, each sudden in onset and cessation, and varying in duration from several minutes to several days. She was first admitted to this hospital in 1924 when a diagnosis of auricular flutter was made. On two occasions the attacks were stopped by the use of quinidine. The cardiac rate was usually above 200 during the period of palpitation. Although several electrocardiograms were obtained while the fast rate was present, it was impossible to determine whether the fundamental rhythm was due to paroxysmal auricular tachycardia or paroxysmal auricular flutter with one to one response.

Five days before her admission in June 1936 while drinking iced water the patient noted the onset of palpitation and vertigo. During the next few days she grew progressively more dyspneic and was unable to sleep.

On admission the temperature was normal, the pulse rate 220 and the respiratory rate 30. Dyspnea and cyanosis were prominent and the neck veins were engorged. There were arteriosclerotic changes in the retinal and peripheral vessels. Chronic bronchitis and emphysema were present, and many medium moist râles were heard at the lung bases. The heart was slightly enlarged. The sounds were of fair quality. The blood pressure was 100 mm Hg systolic and 90 diastolic. The liver was enlarged, but no edema was present. A diagnosis of arteriosclerotic heart disease with congestive heart failure was made.

An esophageal electrode was passed without difficulty. The records obtained showed paroxysmal supraventricular tachycardia and not auricular flutter.

After 25 mg of mechohyl the rhythm reverted to normal, a moderately severe attack of asthma ensued, and auriculo-ventricular nodal rhythm with inversion of the T-waves was present for a short while.

Interpretation of the Electrocardiograms Figure 1 A This is a record showing the three conventional leads. The rate is 75 and the P-R interval 0.13 sec. The QRS complexes are of low amplitude and thickened. Very small biphasic T-waves are present in each lead. B The three conventional leads during an attack are presented here. The rhythm is regular at a rate of 230 per minute. It is difficult to be certain of the presence of any regularly spaced P-waves. C and D A simultaneous recording of Lead II and the esophageal electrogram (C) shows the sharp upstroke of the P-wave and the form of the ventricular complex. Record D taken during an attack shows several points of interest. Whereas in the normal esophageal record auricular activity was present for some time before the excitation wave passed beneath the electrode, the electrode was directly over the origin of the impulse during the tachycardia as the sharp upstroke or "intrinsic" wave is the first evidence of auricular activity. The P-wave falls on the upstroke of the T-wave soon after the termination of QRS complex. The P-R interval is longer than in the previous records. These findings suggest that an auriculo-ventricular nodal paroxysmal tachy-

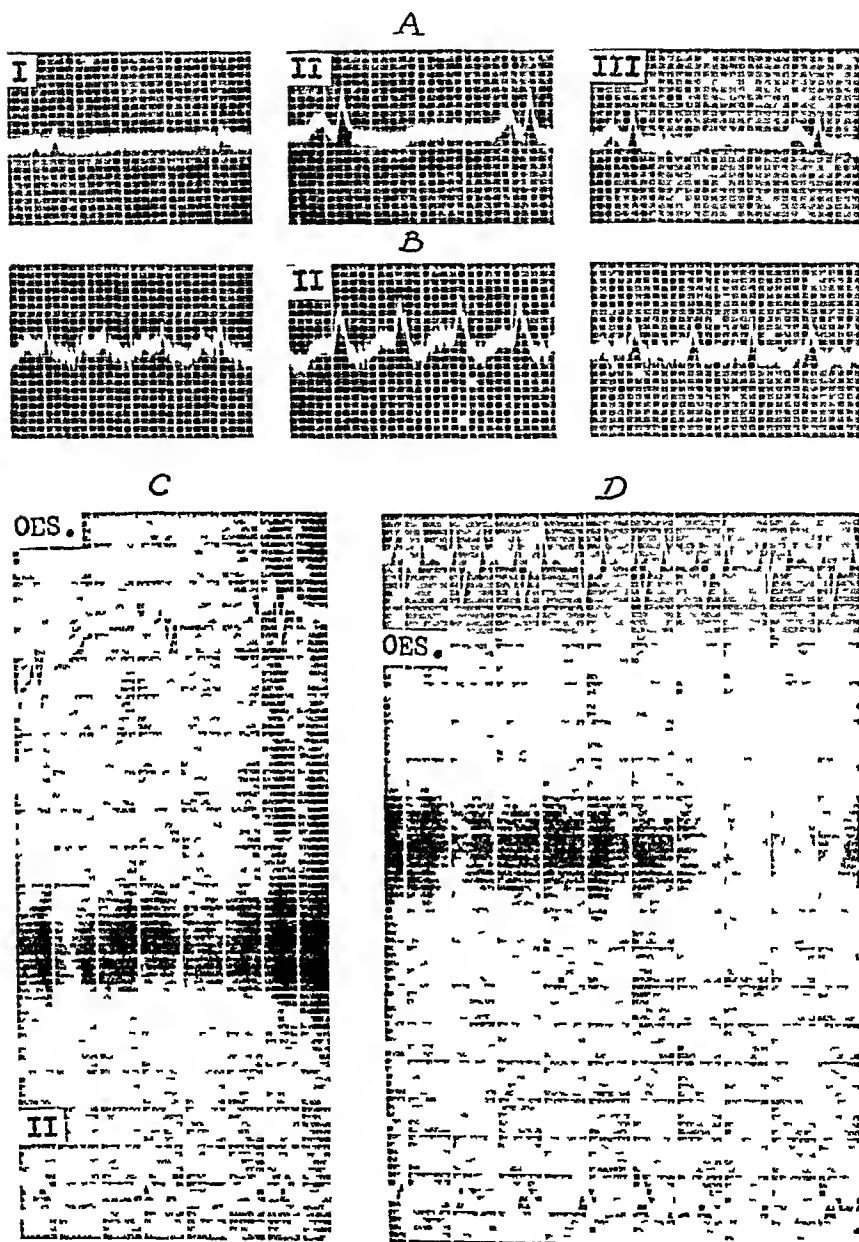


FIG 1 Standardization 1 mv = 5 mm Heavy vertical lines in the curves mark the time in 0.2 sec intervals

cardia is present. One cannot be certain of this, however, as a delayed auriculo-ventricular conduction time is not infrequent in the presence of such a rapid cardiac rate. The form of the QRS complex is the same in each record. Particularly striking is the ease with which the P-waves are visualized in the esophageal curve of record *D* in contrast to the confusion encountered in the simultaneously recorded Lead II.

Figure 2 This unusual record shows the onset of an attack of tachycardia in this patient. The change in the form of the auricular complex with the onset of the fast rhythm is clearly visualized. Lead II is simultaneously recorded.

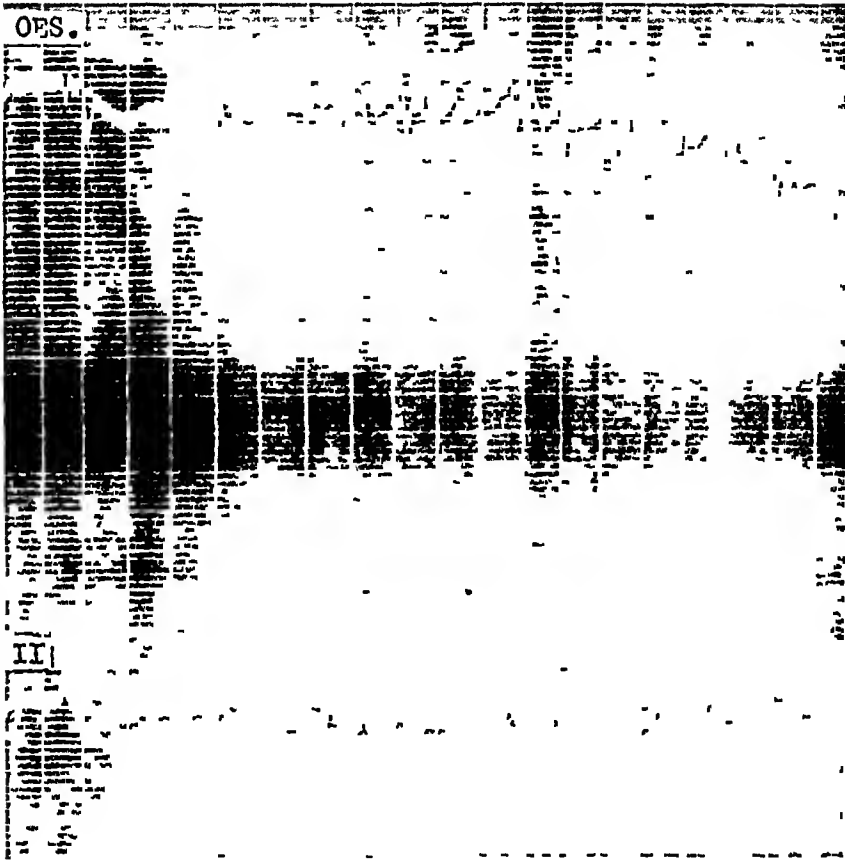


FIG 2

Case 2 Paroxysmal supraventricular tachycardia L B, a 37 year old white housewife, came to the Dispensary in February 1936, complaining of attacks of tachycardia. The attacks began eight years previously, shortly before her marriage. They increased in number during her first pregnancy, and have occurred from three to five times weekly since then. Sneezing, bending over, or any sudden effort usually was the precipitating factor. The tachycardia most often lasted only a few minutes, but occasionally persisted for two or three days. The attacks became more frequent and severe during the month prior to her visit. The past history was non-contributory.

The patient was a well developed and nourished, healthy-looking woman who felt perfectly well when the tachycardia was absent. The general physical examination showed nothing abnormal. The heart was not enlarged. The sounds were of good quality, no murmurs were audible, and the blood pressure was 110 mm Hg systolic and 70 diastolic. A complete diagnostic survey revealed no foci of infection or any causative factor. There was no evidence of organic heart disease.

The patient was able to produce an attack by repeatedly bending over and touching her ankles, thus it was possible to make a complete study of the nature of the tachycardia. It was discovered that light pressure in the region of the right carotid sinus stopped the tachycardia immediately. The patient was taught to perform this simple maneuver. At a visit six months later she stated that no difficulty had been encountered in stopping each attack quickly in this manner.

The Electrocardiograms Figure 3 *B* This record was taken shortly after the cessation of an attack. The rate is 88, and the P-R interval 0.18 sec. The P-waves in Lead II are notched, and the T-waves are all of small amplitude. *A* The electro-

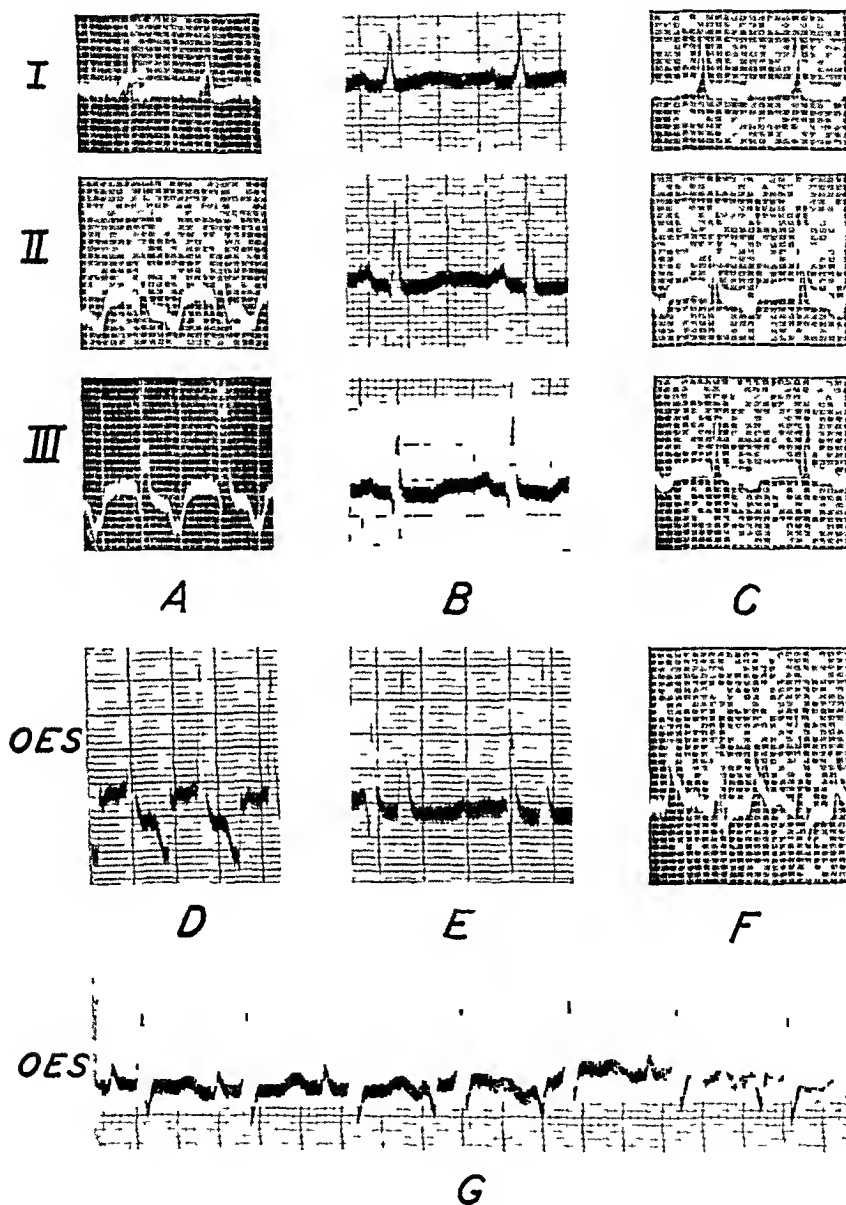


FIG 3

cardiogram during this attack reveals a rate of 150 which is quite regular. In Leads II and III the P-waves are superimposed on the end-deflection of the ventricular complex. The P-R interval is quite definitely longer than in the records taken at a normal rate. *C* This record taken during a second paroxysm shows a P-wave of a different character. The rate is only 136, and the auriculo-ventricular conduction time is slightly longer. These differences suggest that the position of the ectopic focus varied in each of these attacks. *E* In this normal esophageal record the P-waves are quite

distinct *D* and *F* show the form of the esophageal lead in two separate attacks. In each the esophageal electrode was at the same level as in the normal record. In *F* the first evidence of auricular activity is a sharp upstroke while in record *D* changes due to activity at a point away from the electrode are visible before the intrinsic wave appears. *G* This figure furnishes an explanation for the variable form of the records taken during periods of tachycardia. While this esophageal electrogram was being taken the patient held her breath and the position of the electrode remained the same.

The changes in the form of the auricular complexes in successive cycles are apparent. These variations are probably due to a shift in the pacemaker. Thus in this patient there is more than one ectopic focus from which the paroxysms of tachycardia arise.

Figure 4 This attack was promptly stopped by pressure in the region of the right carotid sinus. The characteristic post-paroxysmal pause and the gradual return of the P-R interval to normal are illustrated. An extra-systole (P B) occurred during the pause. Lead II is not clearly recorded as the patient moved while the record was being taken.

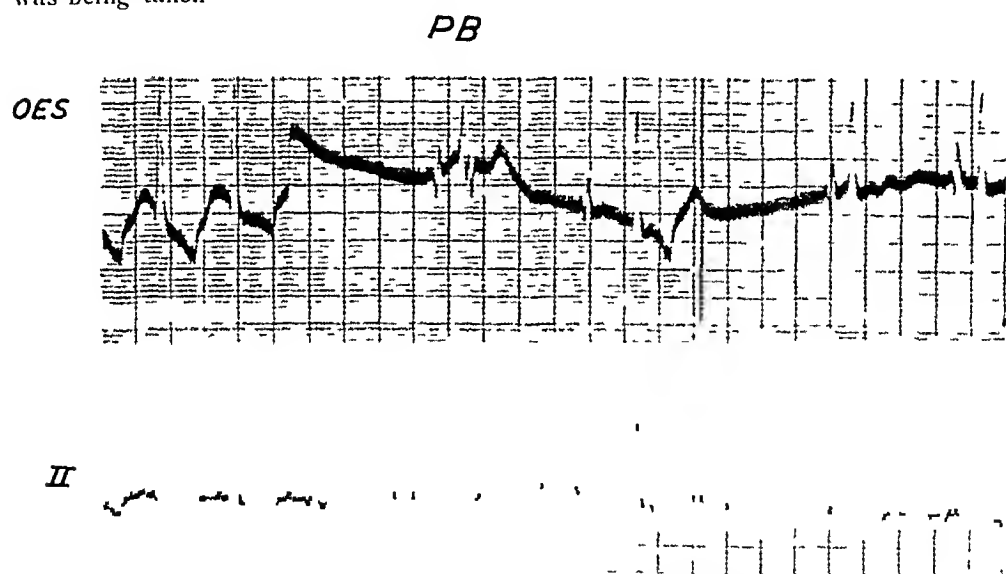
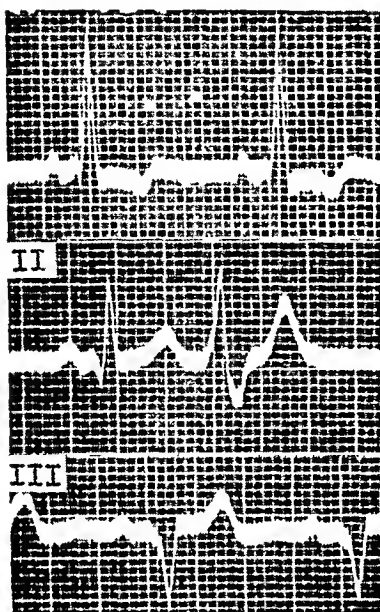


FIG 4 The termination of an attack of paroxysmal tachycardia by carotid sinus pressure

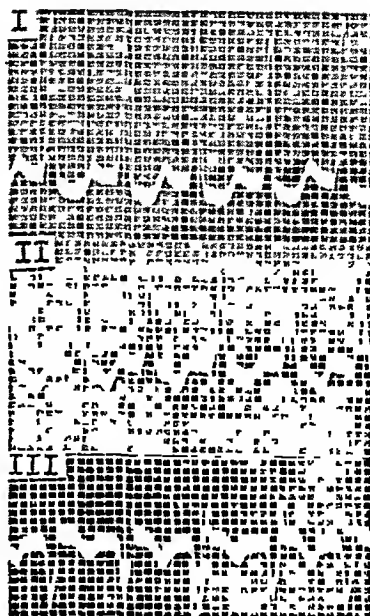
Case 3 Paroxysmal supraventricular tachycardia. F W, a 49 year old white male clerk, had had attacks of paroxysmal tachycardia for a period of 29 years. From the ages of 8 to 12 he had several attacks of rheumatic polyarthritis. The attacks of tachycardia were of sudden onset and termination, lasting from a few minutes to several hours and occurring one to two times a week. They were increased in frequency and duration during periods of constipation and upper respiratory infection. On various occasions the attacks had been stopped by bending over, by a blow to the precordium, or by pressure on the eyeballs.

The patient was well developed and nourished. There were no evidences of cardiac insufficiency. The heart was slightly enlarged both to the right and left. The typical signs of mitral stenosis and aortic insufficiency were noted.

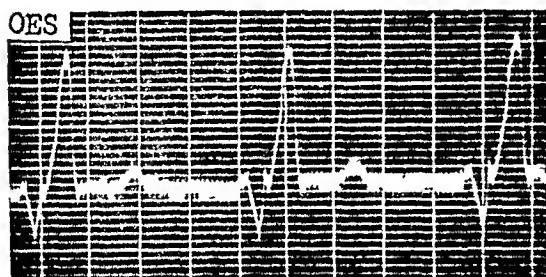
During an attack the rate suddenly increased to 187. The patient's only symptom was palpitation. After electrocardiographic records were obtained the attack was stopped by pressure on the eyeballs. Quinidine has been administered in prophylactic doses, and since that time the attacks have been both less frequent and shorter in duration.



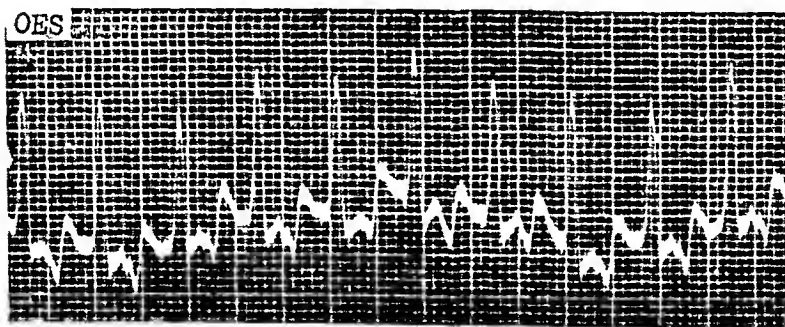
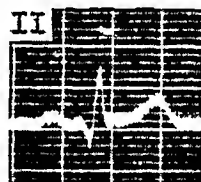
A



B



C



D

FIG 5

Electrocardiograms Figure 5 *A* The normal electrocardiogram shows a rate of 75 with a P-R interval of 0.19 sec. There is a left axis deviation. The QRS complex in Lead III is slurred. T_1 is biphasic, T_2 and T_3 upright. One ventricular extrasystole is present in Lead II. *B* This record taken during a period of paroxysmal auricular tachycardia has a rate of 194. The P-waves and the T-waves are superimposed. The ventricular complexes are supraventricular in type. There is alternation in the amplitude of the QRS complexes. *C* The normal esophageal lead shows a typical auricular complex composed of a small upright wave succeeded by a steep downward deflection as the excitation wave approaches the region in apposition to the electrode. Late in the complex the sharp upstroke or "intrinsic" wave appears. The duration of the intraventricular conduction time is 0.13 second in this record. The simultaneously recorded Lead II shows no such prolongation of the QRS duration. *D* The esophageal electrogram during an attack shows clearly defined P-waves in contrast to the conventional leads. The rate here is only 176. The P-R interval is only 0.15 second as compared to 0.19 in the records with normal rhythm.

Case 4 Paroxysmal ventricular tachycardia. C. S., a 15 year old colored girl, came to the hospital on June 19, 1936 complaining of a sensation of choking and rapid heart action. She had always been healthy. There was no history of tonsillitis, rheumatic fever, or chorea. She stated that in August 1934, and again one year later she had had a similar illness lasting about 10 days. The present attack began one week before admission, and the patient had vomited several times each day.

The temperature was 100.6°, the pulse rate 220, and the respirations 38. The patient was well developed and nourished. She seemed uncomfortable but not acutely ill. The neck veins were a little full, and very rapid venous pulsations were visible. The heart was at the upper limit of normal in size. There was a diastolic shock in the second left interspace, and a prominent pulsation was visible there. The first sound was snapping in quality, and a triple rhythm was present at the apex. There was no evidence of cardiac insufficiency. The remainder of the physical examination was negative.

Following the administration of apomorphine the rate became normal, but the tachycardia reappeared within a few hours. The electrocardiogram revealed a tachycardia which was ventricular in origin. Mecholyl was tried but had no effect. About 24 hours after admission, after one gram of quinidine had been administered, the patient had a sudden stabbing pain over the precordium following which the heart rate became normal. After reversion a systolic apical murmur was audible, but diastole was clear. The roentgen-ray showed an accentuation of the second curve on the left. The position of the barium-filled esophagus was normal indicating that no pronounced enlargement of the left auricle was present. The diagnosis was paroxysmal ventricular tachycardia, with questionable rheumatic heart disease. The patient was discharged and advised to take a prophylactic dose of quinidine daily. No further attacks have occurred.

The Electrocardiograms Figure 6 *A* The record after reversion to normal sinus rhythm shows a rate of 107 with a P-R interval of 0.14 sec. The P-wave in the second lead is of comparatively large amplitude. The QRS complexes in Leads II and III are thickened. There is arching of the S-T intervals and all of the T-waves are inverted. In later records the left axis deviation disappeared, and the T-waves became upright. *B* This record shows the ventricular tachycardia with a rate of 230. No P-waves are visible. *C* and *D* These records show the esophageal electrograms, the first taken while normal sinus rhythm was present. The second taken during an attack shows the striking change which has taken place in the ventricular complexes. Again no auricular waves can be seen. The electrode was at the same level in each instance.

Case 5 Paroxysmal tachycardia of indeterminate origin. A 10 year old col

ored girl came to the hospital on January 2, 1937, because of a rapid heart rate of two hours' duration. There was no history of rheumatic fever or chorea. During the first year of life the patient had had severe rhinopharyngitis complicated by otitis media and later acute tonsillitis with a membrane suggestive of diphtheria. Acute

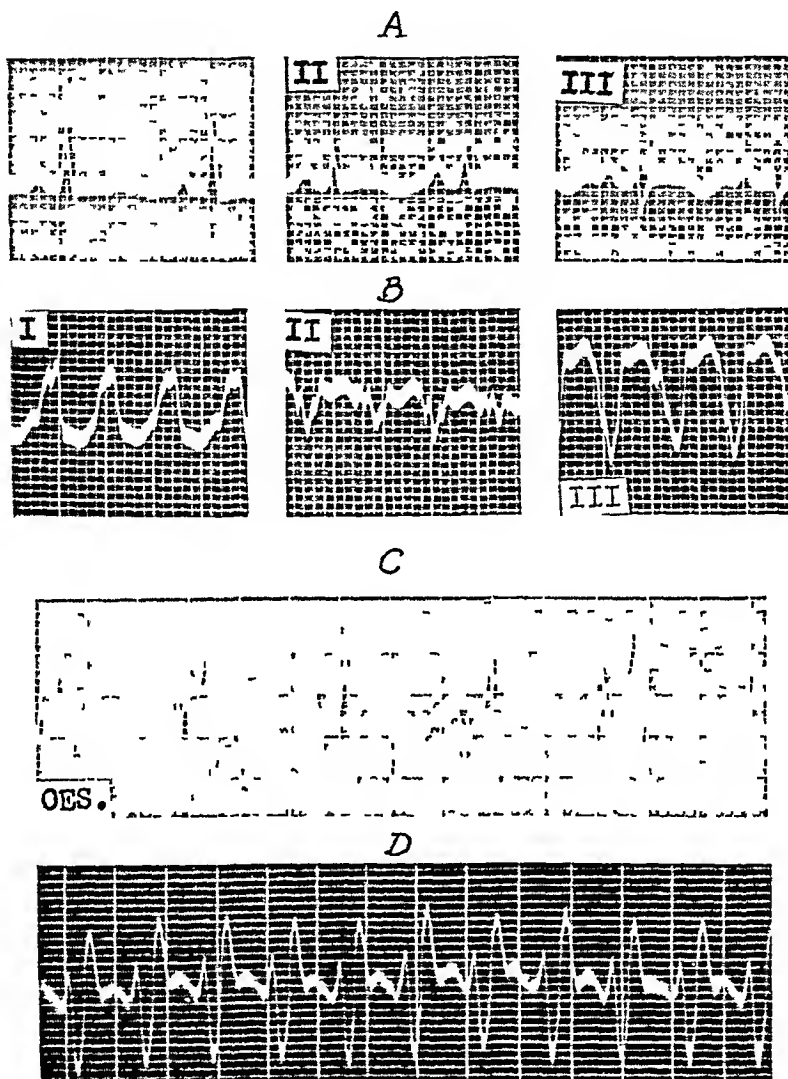


FIG 6

cervical adenitis developed one month later, which had to be drained. At five years of age she had measles and two months later laryngeal stridor which necessitated tracheotomy. Culture of the throat showed *B* hemolytic streptococci but no diphtheria bacilli. An electrocardiogram taken at that time showed frequent ventricular extrasystoles. A tonsillectomy was done later, and the patient was well until April 1935, when she was admitted with lobar pneumonia. The heart was normal. The basal metabolic rate was not elevated.

In June 1936 she came to the hospital complaining of precordial pain. The pulse was so fast that it could not be counted. Before an electrocardiogram could be taken the cardiac rate had dropped to 94. An occasional ventricular extrasystole was present. Following this the patient was quite well until her present attack.

The temperature was normal. The eyes were a little prominent. The tonsils were cleanly removed. The lungs were clear. The heart was not enlarged. During the attack a rapid regular rhythm with a rate of 230 was present. The sounds were of good quality. The neck veins were engorged. The remainder of the examination was negative. When the cardiac rate had returned to normal, no murmurs could be heard.

After the electrocardiograms were taken efforts were made to stop the attack by vagal stimulation such as eye-ball pressure, carotid sinus pressure and finally mecholyl. All were unsuccessful. About five hours after the onset, after 0.3 gm. of quinine sulphate had been given, the pulse rate was found to be 120. It was almost certainly a spontaneous reversion to normal rhythm.

The Electrocardiograms Figure 7. *A* This is the normal record with a rate of 91 and an auriculo-ventricular conduction time of 0.14 second. There is left axis deviation. The T-waves are upright. *B* The normal esophageal electrograms taken at the levels indicated illustrate the sequence of changes in the auricular complex. *C* and *D* These records taken during the period of ventricular tachycardia contrast the ease with which the auricular complex is recognizable in the esophageal record in comparison to the conventional leads. The sharp upstroke is greatest with the electrode placed at 31 cm.

Without further evidence it is impossible to determine accurately whether this tachycardia was ventricular in origin with retrograde P-waves, or auricular with delayed intraventricular conduction. Only by means of a double esophageal electrode to determine the direction of spread of the auricular complex, an electrocardiographic record of the onset or termination of the attack, or by observation of the effect of rebreathing of oxygen on the form of the ventricular complex could further helpful information be obtained. The patient has had no further attacks during which these procedures could be carried out.

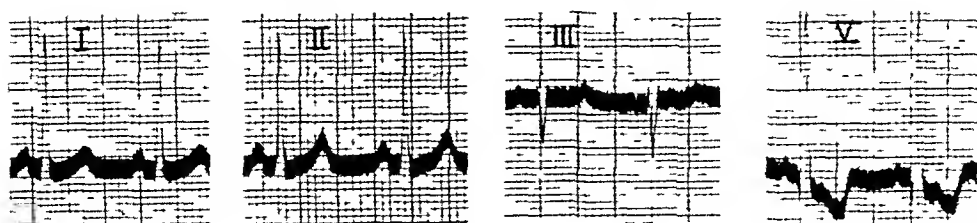
DISCUSSION

The electrocardiographic records taken in these patients demonstrate the greatest ease with which the auricular complex can be recognized during an attack of paroxysmal tachycardia by means of an esophageal lead.

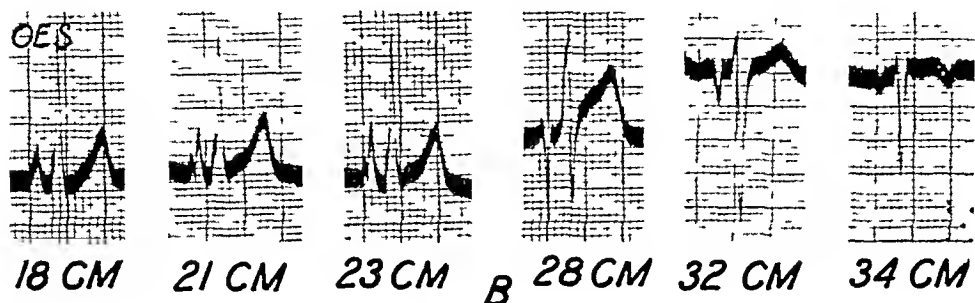
Other methods of amplifying the auricular deflection so that its form could be determined in doubtful cases have been suggested. McGuire and Foulger² in 1931 described three cases in which they used a needle electrode inserted beneath the skin at the second and fifth right intercostal spaces near the sternum. By this means the P-waves were made more prominent, and the true nature of the arrhythmia could be determined.

Roth³ employed a right pectoral chest lead to record tracings of auricular activity. The right arm electrode was placed on the right arm, and the principal or left arm electrode in the right pectoral region. A case of auricular fibrillation and one of mitral stenosis are recorded in which the auricular waves were more clearly visualized than in the conventional leads.

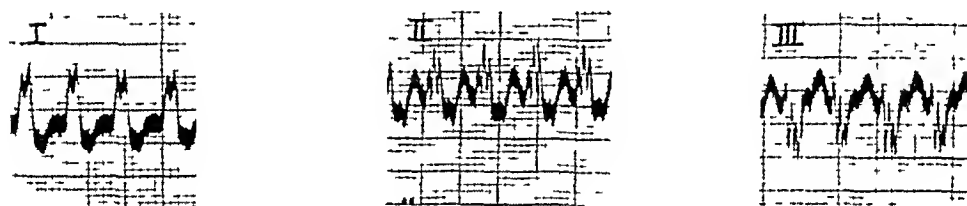
In two of the cases of supraventricular tachycardia included in the present report the auriculo-ventricular conduction time was longer than that recorded during normal sinus rhythm. Although delay in conduction in these cases is not frequent it does occur. It is sometimes difficult to determine definitely whether the abnormal pacemaker is situated in the auricle or whether an auriculo-ventricular nodal tachycardia is present.



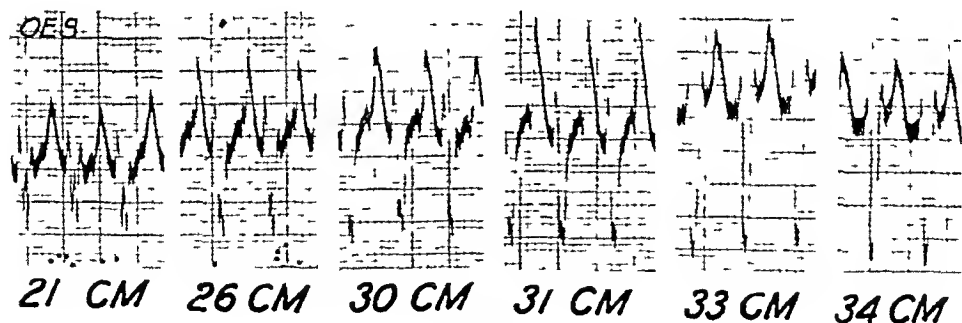
A



B



C



D

FIG 7

Case 2 is of interest because of the shift which occurred in the position of the auricular pacemaker. The form of the P-wave changed conspicuously, but there was only a slight variation in the P-R interval. White⁴ published electrocardiograms illustrating a variation in the position of the pacemaker as shown by the shape of the P-wave, and the length of the P-R interval. In the same report he describes a case of paroxysmal tachycardia.

arising in or very near the sino-auricular node which did not show an absolutely abrupt onset or offset. In case 2, of this series, although the onset and termination were prompt, there was a gradual acceleration of the rate to a maximum level followed by a gradual decline before the termination in some of the attacks. In this case the variation in the rate and the P-R interval in different attacks leads one to believe that there was more than one ectopic focus from which they arose.

In comparison with the incidence of paroxysmal supraventricular tachycardia, cases in which the ectopic focus is in the ventricle are uncommon. In contrast to the former group they are usually associated with organic heart disease, and in many instances occur after coronary thrombosis. The patient reported here was a young colored female in whom no definite organic heart disease could be discovered.

SUMMARY

The esophageal electrogram is helpful in detecting the auricular complexes when these are difficult to outline in the conventional leads.

Three cases of paroxysmal supraventricular tachycardia, one case of paroxysmal ventricular tachycardia, and one of indeterminate origin are presented. The appearance of the normal electrocardiogram and the esophageal electrogram is compared in each case.

Records are shown illustrating the onset and termination of paroxysmal auricular tachycardia. The esophageal lead and the conventional Lead II were recorded simultaneously.

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STUDIES ON EXPERIMENTAL HYPERTENSION

V THE PATHOGENESIS OF EXPERIMENTAL HYPERTENSION DUE TO RENAL ISCHEMIA

By HARRY GOLDBLATT, M D , C M , *Cleveland, Ohio*

THE production of persistent hypertension in dogs and monkeys has been reported in previous communications¹⁻⁴ This was accomplished by constricting the main renal arteries by means of a special silver clamp devised for the purpose In some of the dogs hypertension of severe degree has now existed for more than five years The type of hypertension produced by this method depends upon the degree of constriction of the renal arteries When the constriction is not very great, there is little or no disturbance of renal function accompanying the hypertension and it resembles benign hypertension in man When the constriction is very severe, there is often accompanying damage of renal function which may also be severe Such animals may die in uremia so that in this respect the hypertension resembles malignant hypertension in man Constriction of splenic and of femoral vessels had no effect on blood pressure² This is in keeping with the negative results obtained by Longcope and McClintock⁵ from constriction of the superior mesenteric artery These findings have been confirmed for the dog by other investigators⁶⁻¹⁸ The present report deals with experiments designed to determine the mechanism whereby the reduction of blood flow to the functioning components of the kidney, that is, renal ischemia, induces the development of hypertension

That some pathological change in the kidney may be the cause of some forms of cardiovascular disease in man has been suspected on the basis of clinical observations and pathological findings from the time of Bright^{19, 20} That a pathological change in the kidney may initiate hypertension in man, especially the type that is associated with so-called diffuse vascular disease, has been recognized by some investigators for more than 50 years, since the existence of hypertension was first recognized This view is still upheld by some, like Fahr,²¹ who, on teleological grounds, regards the hypertension as compensatory to the reduced blood flow through the kidney, and by Volhard,^{22a, 22b} on the basis of a humoral mechanism of renal origin, for at least the so-called malignant type of hypertension It is opposed by others, like Kylin,^{23, 24} who does not admit a primary renal origin even for the hypertension that accompanies glomerulonephritis The mechanism whereby the kidneys produce their effect is still regarded as unsolved even by those who

* Presented by invitation, before the American College of Physicians in St Louis, Mo., April 20, 1937

From the Institute of Pathology, Western Reserve University, Cleveland, Ohio
These studies were supported by the Beaumont-Richman-Kohn Fund

consider that these organs can play a primary part in the origin of hypertension

Many experiments have been performed to determine whether the kidneys can be the primary site of origin of hypertension in animals

A SUMMARY OF OTHER EXPERIMENTS DESIGNED TO DETERMINE THE POSSIBLE RENAL ORIGIN OF HYPERTENSION

Bilateral nephrectomy

- Mosler,⁷ (1912) Used rabbits Insignificant elevation of blood pressure
 Backmann,⁸ (1916) Used cats No elevation of blood pressure
 Cash,²⁷ (1926) Used dogs No elevation of blood pressure
 Hartwich,²⁸ (1930) Used dogs No elevation of blood pressure
 Harrison, Blalock and Mason,¹¹ (1936) Used dogs No elevation of blood pressure in 16 out of 18 dogs

Reduction of the amount of functioning renal tissue

- Grawitz and Israel,¹ (1879) Used rabbits Slight hypertrophy of heart, interpreted by the authors as due to hypertension
 Passler and Hemeke,¹⁰ (1905) Used dogs Slight elevation of blood pressure
 Backmann,⁸ (1916) Used cats Slight elevation of blood pressure
 Allen and collaborators,^{31, 32, 33} (1923) Used dogs Slight temporary elevation of blood pressure
 Mark,^{41a, 41b} (1925, 1928) Used dogs Slight elevation of blood pressure
 Anderson,³¹ (1926) Used rabbits No elevation of blood pressure
 Friedman and Wachsmuth,³⁵ (1930) Used dogs No elevation of blood pressure
 Chanutin and Ferris,³⁶ (1932) Used rats Great elevation of blood pressure
 Ryland, D A and Dock, W,³⁷ (1935) Used rats Great elevation of blood pressure

Reduction of amount of renal substance by coagulation necrosis due to ligation of branches of renal arteries

- Janeway,^{38, 39} (1908), assisted by Carrel⁴⁰ Used dogs Slight elevation of blood pressure
 Mark,^{41b} (1928) Used dogs No elevation of blood pressure

Reduction of amount of renal substance by partial renal excision and unilateral nephrectomy combined with coagulation necrosis of part of the remaining kidney by ligation of branches of renal artery

- Cash,⁴² (1924) Used dogs Slight to moderate temporary elevation of blood pressure

- Mark and Giesendorfer,⁴³ (1930) Used dogs Moderate temporary elevation of blood pressure
- Feris and Heynes,⁴⁴ (1931) Used dogs Slight temporary elevation of blood pressure

Destruction of renal substance by irradiation of kidneys with roentgen-rays

- Hartman, Bolliger and Doub,⁴⁵ (1929) Used dogs Moderate elevation of blood pressure
- Page,⁶ (1935) Used dogs Moderate elevation of blood pressure

Renal infarction due to multiple emboli

- Senator,⁴⁶ (1911) Used cats Injected liquid paraffin into renal arteries No rise of blood pressure
- Cash,⁴² (1924) Used dogs Injected insoluble Berlin blue No elevation of blood pressure
- Apfelbach and Jensen,⁴⁷ (1931) Used dogs Injected particles of charcoal into renal arteries No elevation of blood pressure

Occlusion of one main renal artery or its branches

- Friedman and Wachsmuth,³¹ (1930) Used dogs Slight temporary elevation of blood pressure

Occlusion of both main renal arteries

- Katzenstein,⁴⁸ (1905) Used rabbits and dogs No rise of blood pressure
- Cash,²⁷ (1926) Used dogs Moderate to severe elevation of blood pressure

Occlusion (permanent or temporary) of renal arteries, veins and ureters

- Cash,²⁷ (1926) Permanent occlusion Used dogs No elevation of blood pressure
- Loesch,⁴⁹ (1933) Intermittent brief occlusion, every 2 or 3 days Used dogs Moderate persistent elevation of blood pressure

Passive hyperemia (constriction of renal vein) of one kidney

- Pedersen,⁵⁰ (1927), and Bell and Pedersen,⁵¹ (1930) Used dogs Moderate temporary elevation of blood pressure
- Menendez,⁵² (1933) Used dogs Slight temporary elevation of blood pressure in some, none in others

Compression of kidneys by oncometer

- Alwens,⁵³ (1909) Used cats Acute experiments Slight elevation of blood pressure

Permanent obstruction of ureters

- Hartwich,²⁸ (1930) Used dogs Moderate elevation of blood pressure
- Harrison, Mason, Resnik and Ramey,⁵⁴ (1936) Used dogs Moderate elevation of blood pressure

Temporary obstruction of one ureter followed by release of obstruction and excision of other kidney

Rautenbeig,⁷⁵ (1912) Used rabbits Moderate elevation of blood pressure

Effect of nephrotoxic substances

Dominguez,⁷⁶ (1928) Used rabbits Injected uranium salts No elevation of blood pressure except in one animal that developed severe arterial and arteriolar sclerosis, especially in the kidneys

Arnott and Kellar,^{57, 58} (1935, 1936) Used rabbits Injected sodium oxalate Moderate elevation of blood pressure

Scaiff and McGeorge,⁵⁹ (1937) Used rabbits Injected sodium oxalate No elevation of blood pressure

In the earlier investigations summarized above the hypertension that was observed was usually slight and lasted from only a few hours to several days. Some of the later investigators also reported the development of hypertension of slight or moderate degree and of short duration while others succeeded in producing moderate or severe hypertension of longer duration. Under practically every heading contradictory reports occur. These differences are partly due to the various methods, including cardiac hypertrophy, used for determining the existence of hypertension, the various types of animal employed and the slight changes of blood pressure which were regarded as significant by some and not by others. For some of the opposite results there is no obvious explanation. While the results of these experiments do indicate that various pathological changes in the kidneys can, in some way, play a primary part in initiating some degree of hypertension in animals, yet by none of these methods was a condition produced in the kidney which is comparable to that of the kidney in human hypertension that is associated with arteriolar disease. To reproduce a state resembling the condition of the kidney in arteriolar disease, any method must effect a decreased flow of blood to the functioning elements of this organ. Loesch⁴⁹ approximated this condition by completely occluding the circulation to and from the kidneys, and probably the ureter, for a short while, every two or three days, by clamping the entire pedicle of explanted kidneys. However, there is no good reason for believing that such intermittent occlusion of the arterial blood supply to the kidneys as well as complete interference with the return of venous blood from the kidneys reproduces the functional effects of arteriolar disease in the kidney. If the arteriolar disease of the kidney be responsible for the origin of hypertension then the more likely mechanism of its action is persistent reduction of blood flow to the functioning elements of this organ. The only method which would reproduce this exactly is one that would result in functional or organic narrowing of the arterioles of the kidney. No one has yet succeeded in producing either generalized arteriolar sclerosis or arteriolar sclerosis limited to the kidneys. The closest approach, therefore, to the functional effects of arteriolar dis-

ease on the kidneys has been accomplished by reducing the calibre of the main renal arteries alone,¹⁻⁴ with resultant renal ischemia, due to persistent reduction of blood flow into the organs. It was considered possible, therefore, that an elucidation of the mechanism of development of this type of experimental hypertension might make some contribution to our knowledge of the pathogenesis of the hypertension in man that is associated with arteriolar sclerosis and consequent ischemia of the kidneys. This is to be regarded as a preliminary communication on this part of the subject.

EXPERIMENTS

The following experiments were performed for the purpose of elucidating the mechanism of hypertension due to renal ischemia.

Release or Removal of the Clamp In six dogs, one or both clamps were released or removed some time after hypertension due to renal ischemia had

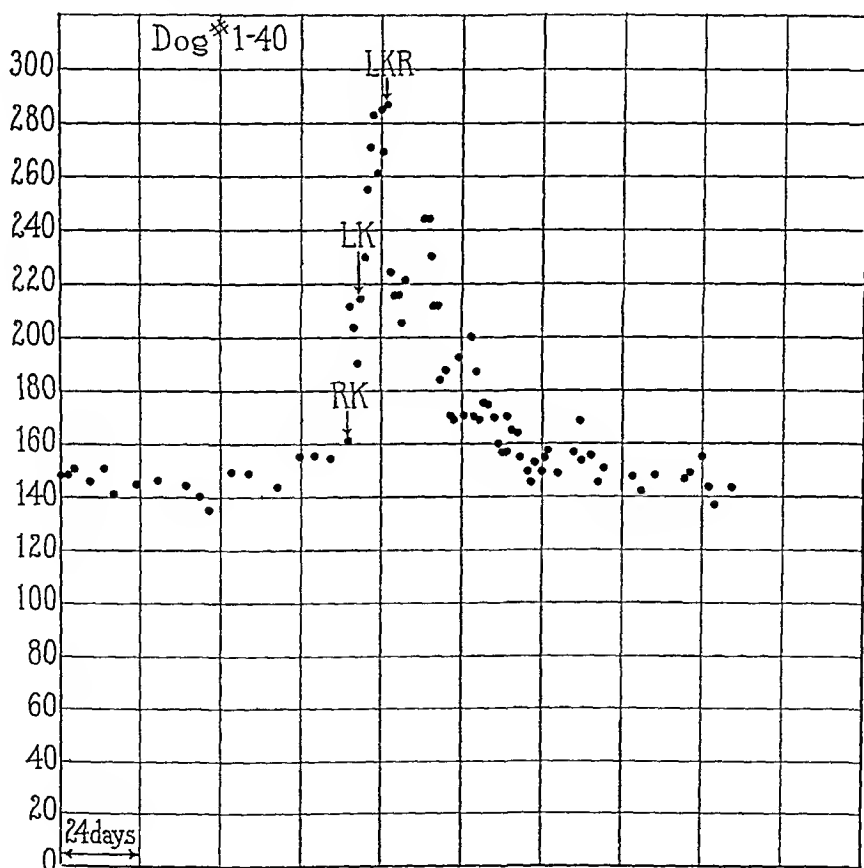


FIGURE 1 Dog 1-40 Female 13.4 Kg

● = Systolic blood pressure, van Leersum carotid loop method RK = Right main renal artery severely constricted LK = Left main renal artery severely constricted LKR = Left clamp completely released but left on the artery

The blood pressure, which had risen to a very high level after the constriction of the second renal artery, fell to normal in about one month after the release of the clamp on this artery.

been established. Quite promptly, but after a variable period, the blood pressure in these animals returned to the original level. In Dog 1-40 (figure 1), release of one clamp was followed by a rather slow fall of the blood pressure to the original level. In this animal there was no impairment of renal function. In Dog 2-67 (figure 2), after unilateral nephrectomy (LN), severe constriction of the main artery of the remaining kidney (RK₁) resulted in severe hypertension and severe impairment of renal function. When the clamp was released, (RKR₁) blood pressure and renal function promptly returned to normal. Reconstriction of the artery (RK₂) again resulted in hypertension and uremia. Slight release of the constriction (RKR₂) relieved the uremia but the blood pressure remained slightly elevated.

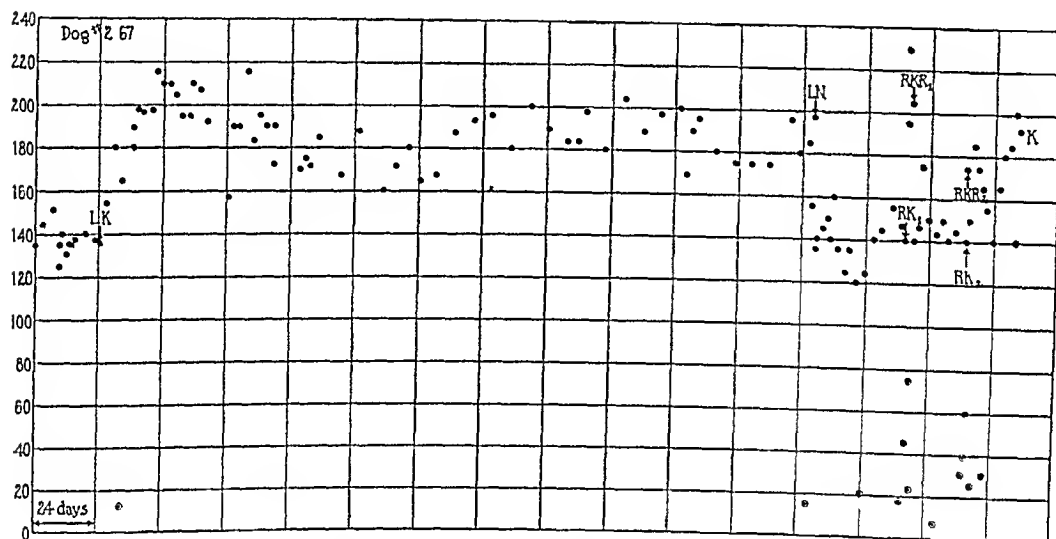


FIGURE 2 Dog 2-67 Female 136 Kg

● = Mean blood pressure, mm Hg, ○ = blood urea mg per 100 cc plasma. LK = Left main renal artery severely constricted. The blood pressure became greatly elevated. During about ten months after this the blood pressure remained elevated but gradually fell to a moderately elevated level. LN = The ischemic left kidney was excised and the blood pressure promptly fell to the normal level. RK₁ = The right main renal artery was severely constricted. The blood pressure became elevated and uremia developed. RKR₁ = The clamp on the right main renal artery was released. The blood pressure, blood urea, creatinine and non-protein nitrogen promptly returned to normal. RK₂ = The right main renal artery again constricted. Elevated blood pressure and uremia again resulted. RKR₂ = The right main renal artery partly released. Blood pressure dropped temporarily, then rose again and remained elevated. The animal developed severe uremia. K = Killed.

Removal of the Ischemic Kidney During the Period of Hypertension Following the Constriction of One Main Renal Artery. It was shown in the original communications^{1,2} that hypertension of some degree follows the constriction of the main renal artery of only one kidney but that after a variable period the blood pressure tends to return to the original level. In some dogs the blood pressure remains elevated for a considerable period following unilateral renal ischemia. In one dog, 2-67 (figure 2), the mean

blood pressure remained at a higher level than normal for about nine months following the constriction of the main renal artery of only one kidney. During this period there was no impairment of renal function. After the removal of this kidney (LN) the blood pressure promptly fell to the normal level. Severe constriction of the main renal artery of the remaining kidney

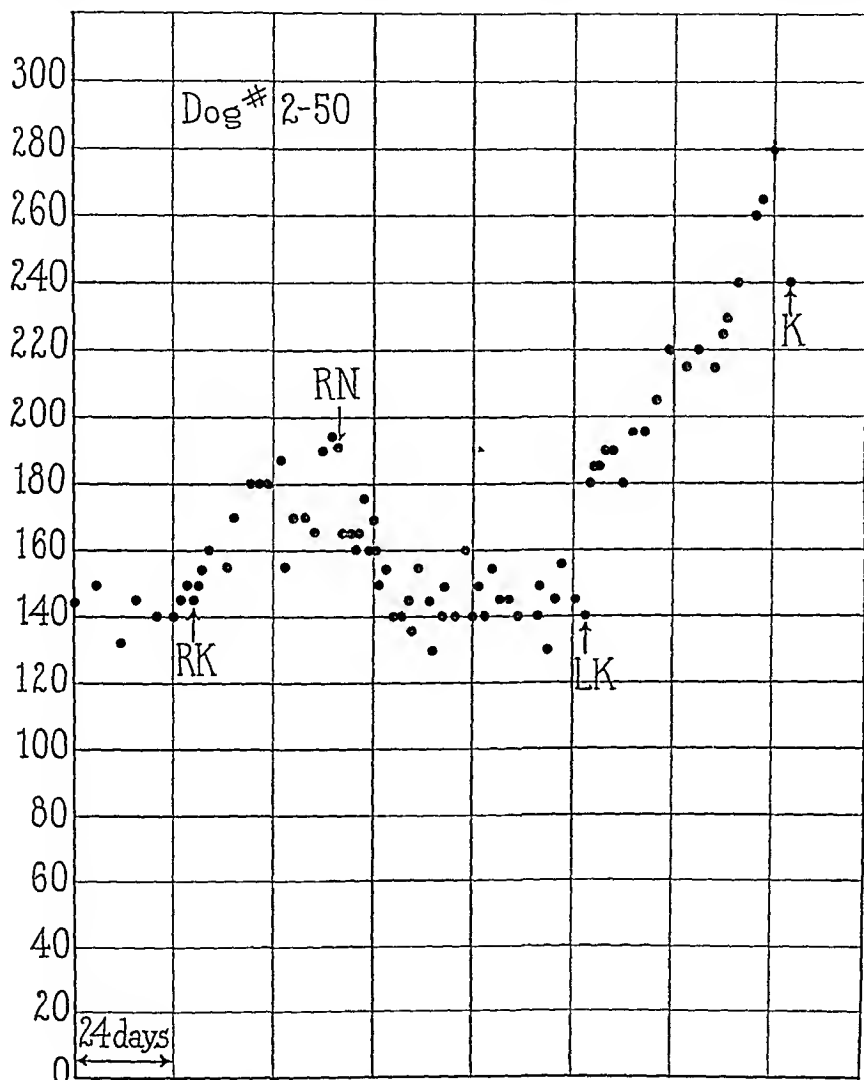


FIGURE 3 Dog 2-50 Female 17.8 Kg

● = Mean blood pressure, mm Hg RK = Right main renal artery moderately constricted RN = Right nephrectomy at a time when the mean blood pressure was elevated resulted in its prompt return to normal LK = Severe constriction of main renal artery of left kidney This was followed by very high elevation of mean blood pressure + = The mean blood pressure at this time was more than 300 mm Hg K = Killed

(RK₁) resulted in reelevation of mean blood pressure and impairment of renal function. In two other dogs also, at the height of elevation of blood pressure, after moderate to severe constriction of the main renal artery of one kidney, this ischemic kidney was excised. Dog 2-50 (figure 3), illus-

trates what happened in these animals. As in the case of Dog 2-67 (figure 2), removal of the ischemic kidney (RN) was followed by a prompt return of the mean blood pressure to the original level. Constriction of the main renal artery of the remaining kidney (LK) was followed by a prompt re-elevation of blood pressure which persisted. The results of these experiments indicate the importance of ischemia as the pathologic change and the kidney as the primary site of origin of this type of hypertension.

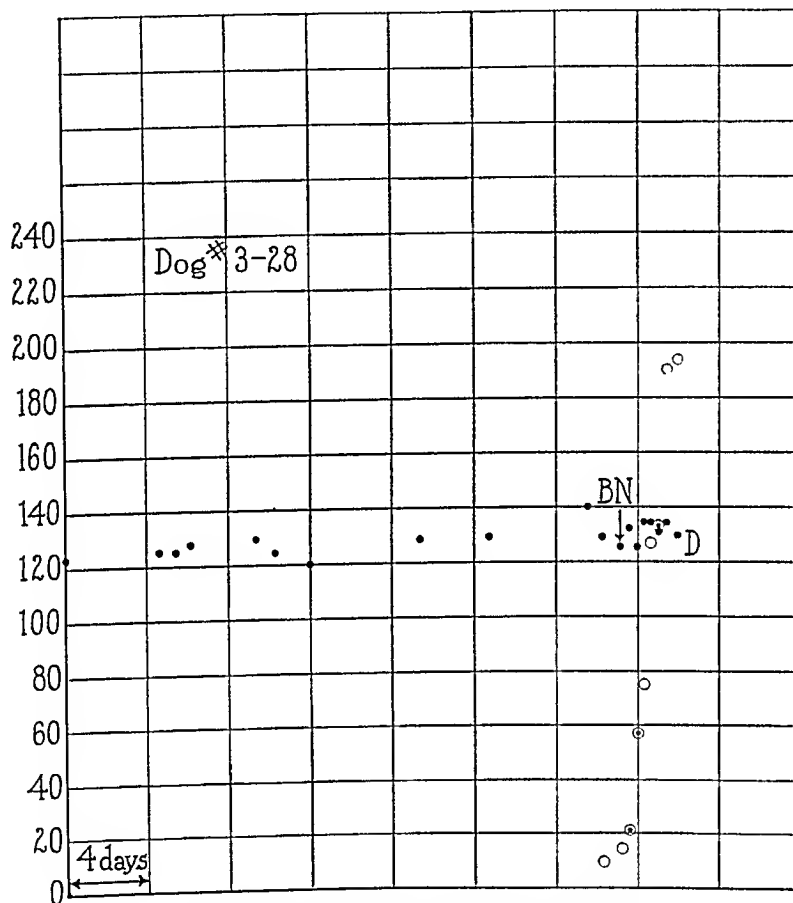


FIGURE 4 Dog 3-28 Male 166 Kg

● = Mean blood pressure, mm Hg ○ = Blood urea nitrogen mg per 100 c.c. plasma
BN = Bilateral nephrectomy The blood pressure did not become elevated D = Died

Bilateral Nephrectomy If uremia alone were the cause of hypertension, then the removal of both kidneys, which is always followed by the development of uremia, should also, invariably, be followed by the development of hypertension.

In five dogs, both kidneys were removed. In three, bilateral nephrectomy was performed at one time and in two, the nephrectomies were separated by an interval of a week or longer. Most of the animals appeared in good condition for about 48 hours following the operation. All the animals died.

in uremia but the blood pressure did not rise during the period of survival which varied from two to five days. Figure 4, Dog 3-28, illustrates one of these experiments. This finding is in keeping with the results obtained by other investigators^{11, 25, 26, 27, 28}

Occlusion of the Main Renal Artery of Both Kidneys It might be considered that occlusion of both main renal arteries would be equal to, and give the same results, as bilateral nephrectomy. This is not the case. In

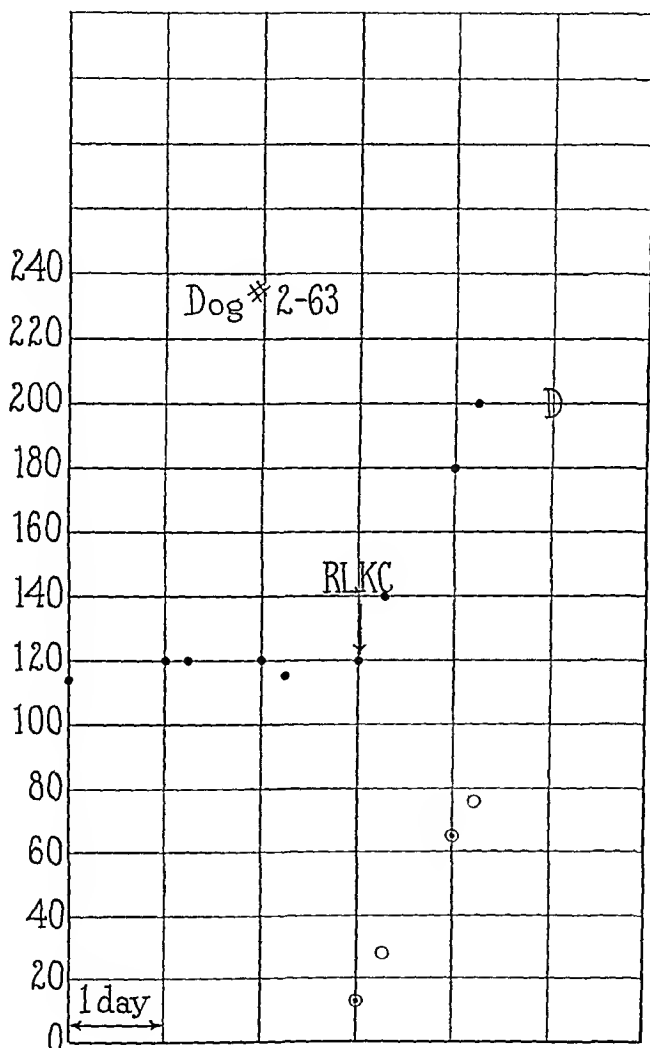


FIGURE 5 Dog 2-63 Female 162 Kg

● = Mean blood pressure, mm Hg ○ = Blood urea, mg per 100 cc of plasma
 RLKC = Both main renal arteries occluded The blood pressure rose to quite a high level
 D = The animal died in uremia

four dogs the main renal artery of both kidneys was clamped completely at one operation and in two dogs the occlusion of the second artery was carried out after an interval of a week or longer. The complete occlusion of one

main renal artery was not followed by either uremia or a significant elevation of blood pressure. In all four animals, however, simultaneous occlusion of the main renal artery of both kidneys was followed by the development of severe uremia and slight or moderate elevation of the blood pressure. The degree of hypertension in the animals with both renal arteries occluded was not as great as in dogs with both main renal arteries only moderately or

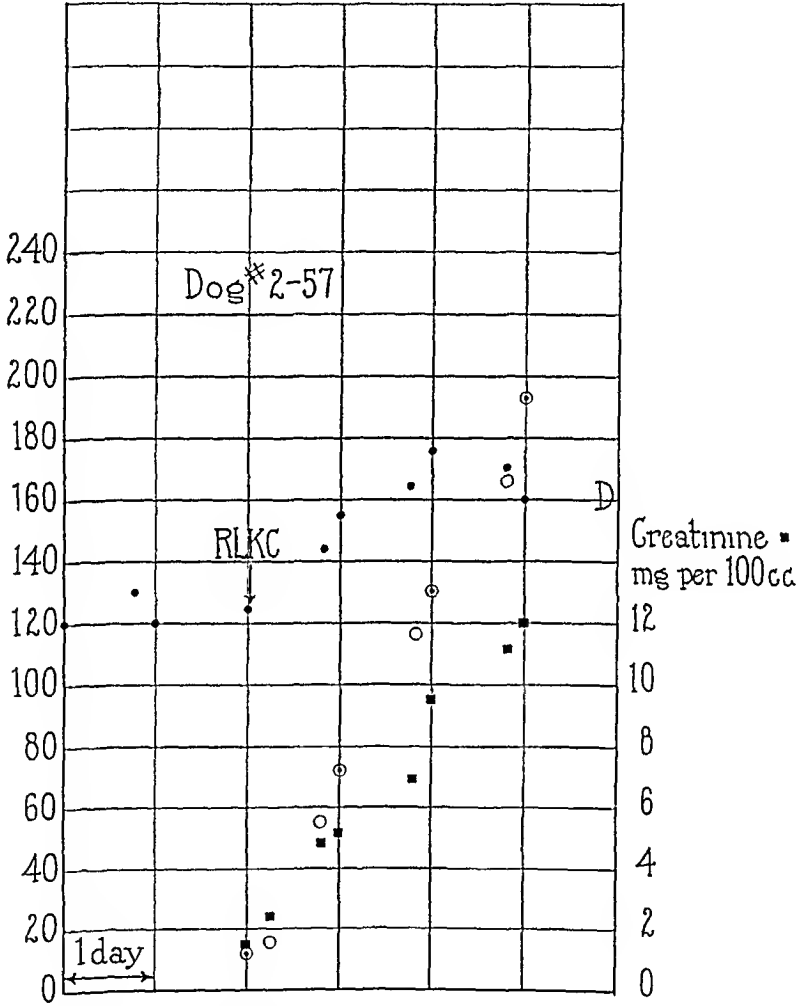


FIGURE 6 Dog 2-57 Female 18.4 Kg
● = Mean blood pressure, mm Hg ○ = Blood urea, mg per 100 cc of plasma
■ = Blood creatinine mg per 100 cc of plasma RLKC = Right and left main renal arteries occluded The blood pressure showed a moderate elevation following the occlusion of the arteries D = The animal died in uremia

severely constricted. The period of survival was about the same as that of the bilaterally nephrectomized animals. In the animals with both main renal arteries occluded, as in those bilaterally nephrectomized, the shock of the operation was evidently not great and for about 48 hours they seemed in

excellent condition Both groups survived about the same period and all developed severe uremia, yet the animals with both arteries occluded did show a significant elevation of blood pressure which is illustrated for three of the dogs in figures 5, 6 and 7, while the nephrectomized animals failed to show a rise of blood pressure In Dog 2-65, as a control, all of the arteries to the spleen were tied off completely (figure 7), some time before

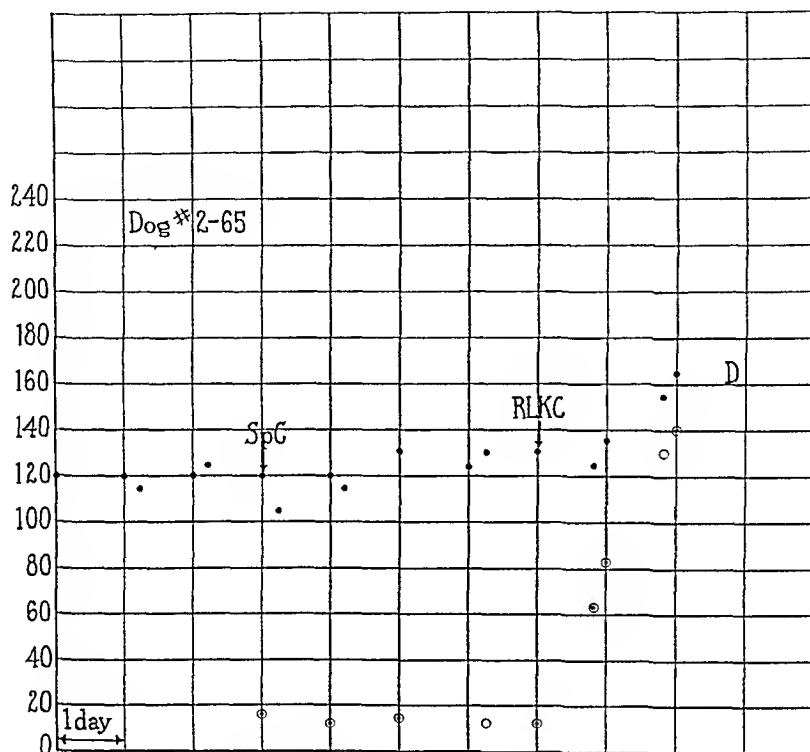


FIGURE 7 Dog 2-65 Female 152 Kg

● = Mean blood pressure, mm Hg ○ = Blood urea nitrogen mg per 100 cc of plasma SpC = Splenic arteries occluded There was no significant rise of blood pressure after this procedure RLKC = Right and left main renal arteries occluded After this there was a moderate elevation of blood pressure D = The animal died in uremia

the renal arteries were occluded The occlusion of the splenic vessels was not followed by a significant elevation of mean blood pressure When both main renal arteries were occluded (RLKC) (figure 7), the blood pressure became slightly elevated severe uremia developed and the animal died

That a dog can survive for a long time the occlusion of both main renal arteries, provided the occlusion is not accomplished abruptly, has been well shown by four animals, in which the occlusion was accomplished in two or more stages One dog has proved this very strikingly At the second clamping of both main renal arteries carried out successively about one year after the initial partial constriction both main renal arteries were occluded This animal survived the complete occlusion of both main renal arteries for four years Hypertension of severe degree persisted during the entire

period and renal function, as shown by urea clearance, was only slightly affected. At autopsy, one kidney was very small and the other only moderately reduced in size. No accessory arteries were found except those that entered the kidney through the capsule. Other experiments of this kind, to be reported later, are being carried out to determine the exact source and extent of the supply of blood to such kidneys.

DISCUSSION

As in the case of partial constriction of both main renal arteries,² the hypertension which follows occlusion of both main renal arteries can be explained by a possible nervous reflex from the kidney by way of the central nervous system to the peripheral vasomotor apparatus or by some humoral mechanism, or by a combination of both mechanisms.

That hypertension due to occlusion of both renal arteries is not due to a nervous reflex from the kidney is indicated by the fact that in some of these animals the renal pedicle was carefully denervated before the clamp was applied. It has also been shown by other investigators,^{6, 10} and we have confirmed this, that renal denervation does not interfere with the development of experimental hypertension due to partial constriction of the main renal arteries. Section of the splanchnic nerves in the thorax, combined with excision of the lower four thoracic sympathetic ganglia, does not interfere with the development of hypertension or permanently reduce the hypertension produced by renal ischemia.⁴ In an investigation soon to be published in collaboration with Dr. W. B. Waitman, it will be shown that section of the anterior nerve roots, from the sixth dorsal to the second lumbar inclusive, also does not interfere with the development of hypertension or permanently reduce the hypertension produced by renal ischemia. Finally, Freeman and Page¹⁰ have shown that total sympathectomy does not interfere with the development of hypertension due to bilateral renal ischemia. These results are not to be interpreted as evidence or proof that the surgical procedures being practised on human beings with hypertension are not justifiable and that no improvement is to be expected from these procedures. What they do show is that in experimental hypertension, due to the permanent renal ischemia effected by the clamps, section or excision of various portions of the nervous system controlling a large part of the vasomotor mechanism of the abdominal organs, does not result in prevention or reduction of this type of experimental hypertension. These experiments serve to emphasize the importance of the reduction of the circulation to the functioning components of the kidney rather than a primary effect on the general vasomotor mechanism of the abdomen as the cause of this type of hypertension. This is in keeping with the views of Prinzmetal and Wilson⁶¹ and of Pickering⁶² about the secondary part played by the vasomotor mechanism in human hypertension. In man it is at least possible that as a result of some or all of the surgical procedures being practised on the

nervous system for the cure of hypertension, actual improvement of the circulation to the functioning components of the kidney may occur. Dilatation of renal arterioles without fixed organic changes in their walls might occur in some cases, as a result of these procedures. Since, in man, there is frequently no narrowing of the large renal vessels to interfere with the flow of blood into the kidney, it is at least conceivable that improved circulation to the functioning components of the kidney may follow as a result of dilatation of arterioles. This improvement of renal circulation could then account for the fall of blood pressure which has been observed in about the same rather small percentage of cases treated by the various surgical procedures on the nervous system. This view is in agreement with that of Peet⁶⁹ on the mode of action of resection of the splanchnic nerves in lowering the blood pressure in human beings with hypertension. It is not, however, the view that is generally accepted by those who have been performing operations on the nervous system for the cure of hypertension in man⁶³⁻⁷⁵. They prefer to regard the improvement following section or excision of the nerves as due to the elimination of their control over the corresponding portion of the vasomotor mechanism. The same improvement of the circulation cannot happen, or can happen to only a very limited degree, as the result of increased dilatation of the arterioles in the experimental kidney, as long as the main renal artery remains constricted by the clamp. These observations do minimize the importance of the effect of the vasoconstrictor mechanism in the abdomen in hypertension due to renal ischemia, because the removal of this mechanism by the various surgical procedures does not prevent or cure the hypertension as long as the clamps remain applied and the blood flow to the functioning components of the kidneys remains unimproved.

If the mechanism whereby constriction of the main renal arteries produces its effect on blood pressure be humoral and of renal origin then, in the case of the hypertension which also follows occlusion of both main renal arteries, it must be assumed that the natural accessory circulation through the capsule which may become more prominent in these circumstances, is sufficient to wash some hypothetical "effective substance" into the systemic circulation through the main renal veins. The term "effective substance" will be used in this paper to avoid commitment to the existence of a direct pressor substance rather than one which acts indirectly to produce the pressor effect. The effective substance, for example, might act synergistically with a known pressor hormone from an endocrine organ, such as the hypophysis or adrenal. It is also possible for the hypothetical effective substance from the kidney to act by sensitizing the contractile elements of the arterioles to the action of the pressor hormone or the reverse may be the case. The effective substance might also produce its effect by neutralizing or reducing the amount of a hypothetical depressor substance circulating in the blood. That there may be an effective substance from the kidney is indicated by

reports of the pressor effect of extract of ischemic kidneys from dogs with experimental hypertension,^{11, 13, 17} and of arteriosclerotic kidneys¹³ from human beings with hypertension. However, the results of such investigations should be interpreted with caution because a pressor effect has also been obtained with extracts of normal kidneys^{118, 119} and with extracts of various

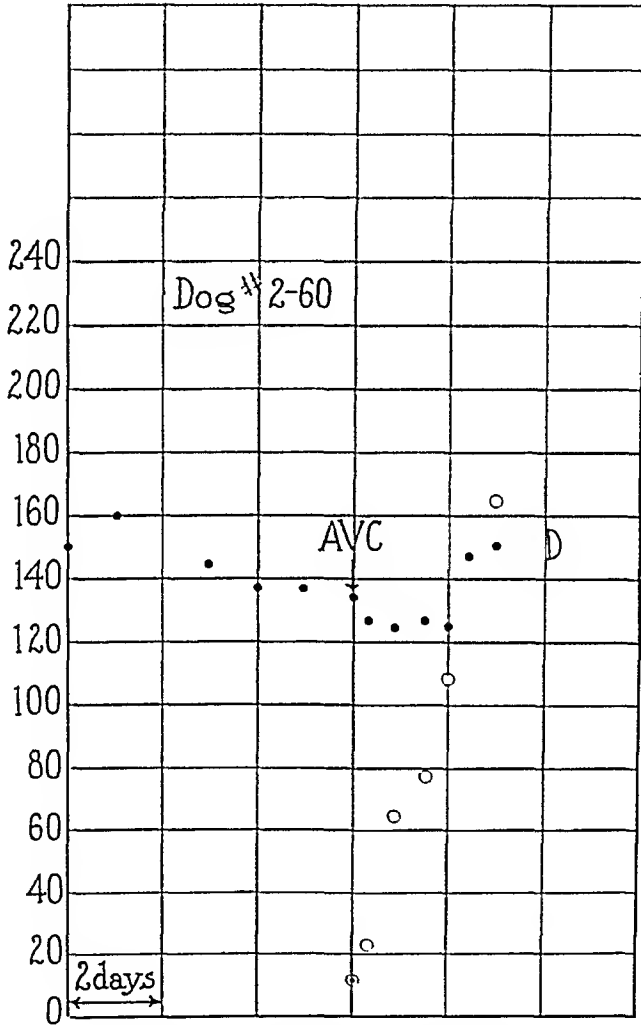


FIGURE 8 Dog 2-60 Male 16.6 Kg

● = Mean blood pressure mm Hg ○ = Blood urea nitrogen mg/100 cc plasma
 AVC = Both main renal arteries and veins occluded The blood pressure did not become elevated D = Died

other normal organs¹²⁰. The existence of a pressor substance in the systemic or renal vein blood of animals with hypertension due to renal ischemia has not been demonstrated¹² and no greater quantity of pressor substance than the normal has been found¹² in the extract of plasma of dogs with this type of experimental hypertension. It has not been proved that the systemic

blood, spinal fluid, or urine of human beings with hypertension of any type invariably contains a pressor substance. Many reports of the finding of a pressor substance⁷⁰⁻¹⁰⁴ and of the failure to find a pressor substance¹⁰⁵⁻¹¹⁷ have been published. A discussion of these results would serve no useful purpose here. The pitfalls of such investigations were well shown by O'Connor¹²⁶. The burden of the proof still rests with those who claim the

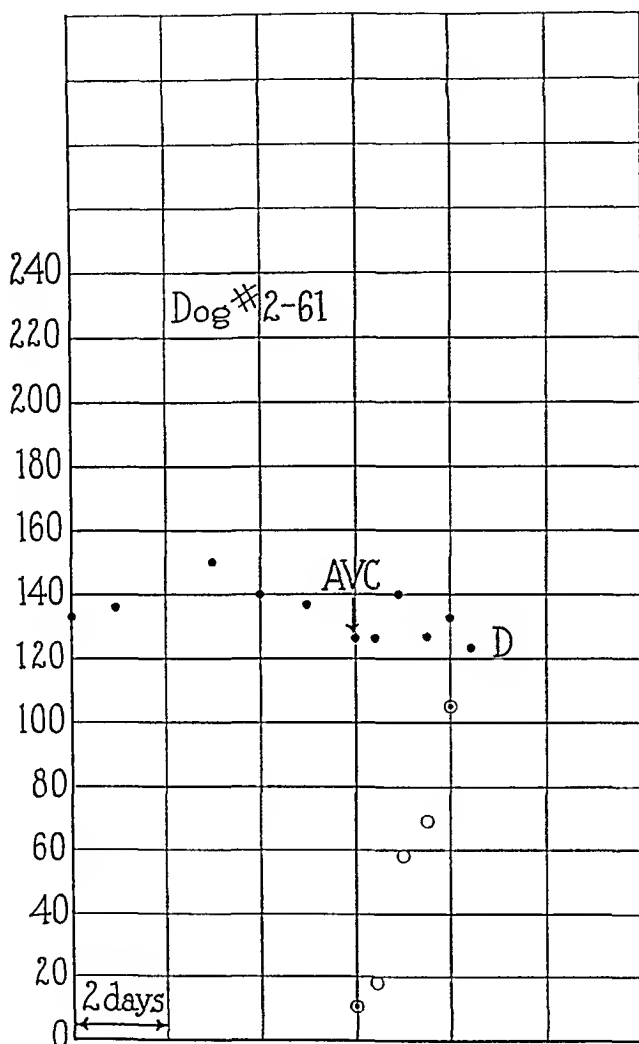


FIGURE 9 Dog 2-61 Female 148 Kg

● = Mean blood pressure mm Hg ○ = Blood urea nitrogen mg per 100 c.c. plasma
 AVC = Both main renal arteries and veins occluded The blood pressure did not become elevated D = Died

invariable presence of an unusual amount of a known pressor hormone or of a new kind of pressor substance in pure or extracted blood, spinal fluid or urine of human beings with hypertension, especially the so-called benign or essential type. The experiments which follow are part of an investigation

that is being carried out to determine the part played by a possible humoral mechanism in the pathogenesis of hypertension due to renal ischemia

Constriction or Occlusion of Both Main Renal Arteries with Simultaneous Occlusion of Both Main Renal Veins One obvious but indirect way of testing for a possible humoral mechanism originating in the kidney is to constrict or occlude the main renal arteries, procedures which are now known to produce hypertension, and, at the same time, to occlude the main

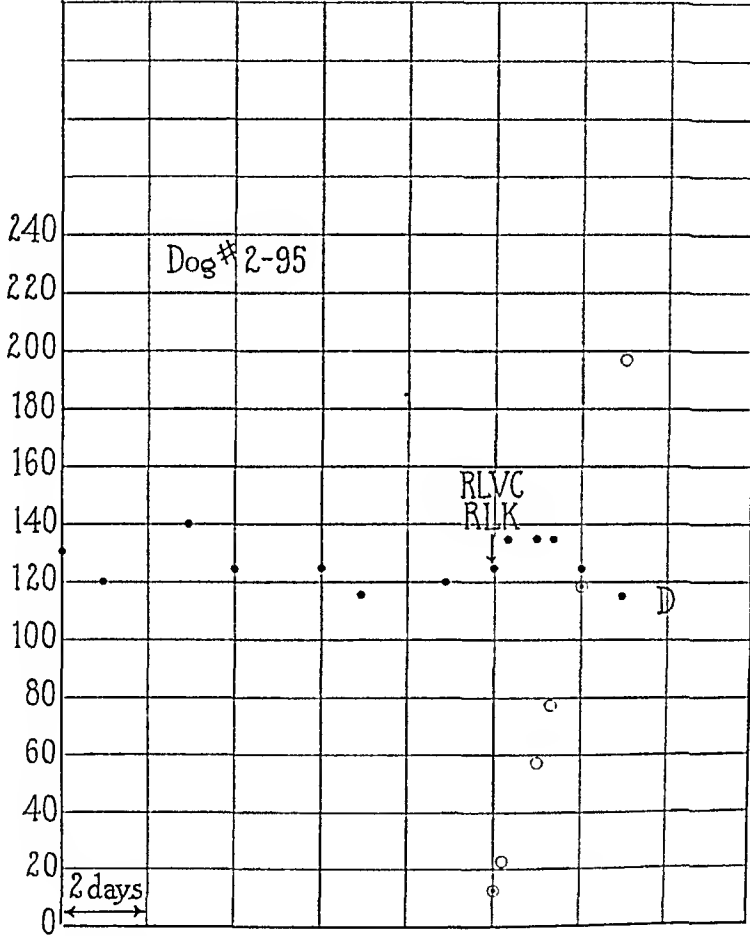


FIGURE 10 Dog 2-95 Female 16.4 Kg

● = Mean blood pressure mm Hg ○ = Blood urea nitrogen mg per 100 cc RLVC = Both main renal veins occluded RLK = Both main renal arteries severely constricted
The animal died in uremia but the blood pressure did not become significantly elevated

renal veins in order to prevent the hypothetical effective substance from leaving the kidneys. Failure of development of hypertension would be evidence in favor of a humoral mechanism originating in the kidney as the cause of the hypertension.

In two dogs (2-60 and 2-61) the main renal arteries and veins of both kidneys were occluded at one time. The blood pressure and some of the

chemical changes in the blood of these dogs are illustrated in figures 8 and 9. Both developed severe uremia but no rise of blood pressure occurred during the short period of survival. These results are in keeping with those of Cash²⁷ who found that no elevation of blood pressure occurred in dogs after the permanent occlusion of both main renal arteries, veins and ureters.

In two dogs (2-51 and 2-95) the main renal veins were occluded and the main renal arteries were only severely constricted. The animals developed severe uremia but no elevation of blood pressure occurred during the short period of survival. Figure 10 illustrates the blood pressure and chemical changes in the blood of one of these animals, Dog 2-95.

Since it has been shown that the permanent constriction or occlusion of the main renal arteries alone is followed by a definite rise of blood pressure, these results may be interpreted as indicating the probable interference with the entrance of the hypothetical effective substance into the systemic circulation by way of the renal veins.

III. PART PLAYED BY ENDOCRINE ORGANS IN THE ORIGIN OF HYPERTENSION DUE TO RENAL ISCHEMIA

As part of the study of the humoral mechanism, an attempt has been made to investigate the part played by the endocrine organs that are known to produce a vaso-pressor hormone.

Hypophysis. Page²⁸ has shown that in dogs, hypophysectomy does not prevent the development of experimental hypertension due to renal ischemia, but that it does reduce the blood pressure in some animals with this type of hypertension. The significance of these contradictory findings cannot be evaluated at the present time. More experiments of this kind should be performed. The effect on this type of hypertension of removal of the various portions of the pituitary body have not yet been investigated.

Adrenals. In a previous communication² an experiment on Dog No. 8-9 was described in which excision of the right adrenal, the destruction of the medulla of the left adrenal, denervation of this adrenal and section of the left splanchnic nerves in the abdomen did not prevent the development of hypertension after the renal arteries were moderately constricted. The only conclusion that can be drawn from this experiment is that hypertension can develop in the absence of the medulla of both adrenal glands, as a consequence of renal ischemia, and that the presence of the medulla of the adrenal is not necessary for the development of this type of hypertension. Since then other experiments have been performed which were designed to determine the part which the cortex of the adrenal gland may play in the development of experimental hypertension due to renal ischemia. This is in the nature of a preliminary communication on this subject. The study is being continued and full details, including chemical studies, will be published later in collaboration with Dr. R. F. Hanzal. Up to the present time the following experiments have been performed.

Bilateral Adrenalectomy, without Supportive or Substitution Therapy and Renal Ischemia In this group of animals no supportive (sodium chloride and sodium bicarbonate or sodium citrate by mouth) or substitution (intra-venous cortical extract *) therapy was given after the removal of both adrenals

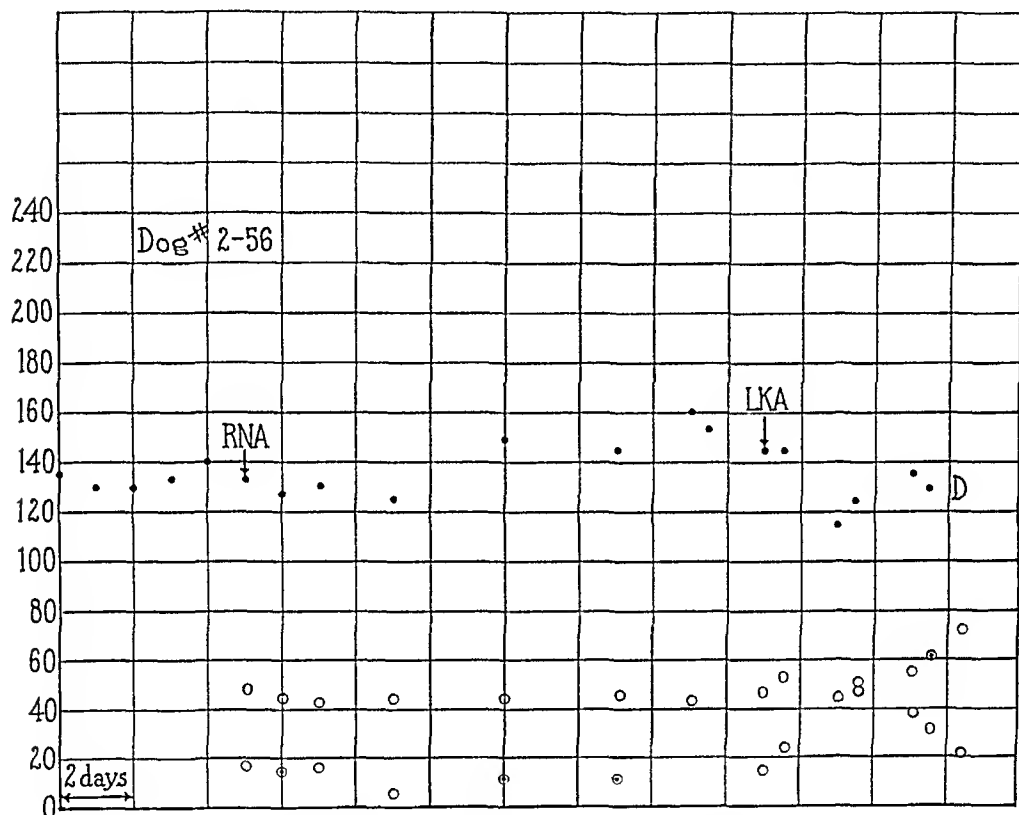


FIGURE 11 Dog 2-56 Female 232 Kg

● = Mean blood pressure, mm Hg ○ = Blood urea nitrogen mg per 100 cc of plasma ○ = CO₂ combining power, volumes per 100 cc RNA = Right adrenalectomy and right nephrectomy If anything, a slight elevation of blood pressure occurred after these procedures LKA = Left adrenalectomy and left main renal artery severely constricted The animal developed uremia and the blood pressure fell D = The animal died in uremia

In three dogs, both main renal arteries were permanently constricted at the time of the second adrenalectomy In two of these (2-56 and 2-62) the first adrenalectomy preceded the second by about two weeks, but in one animal the adrenalectomy and the constriction of both main renal arteries were carried out at the same time (Dog 3-22) The blood pressure did not become elevated in any of these animals, but the period of survival was short (Figure 11)

* The cortical extract used in these experiments was Eschatin which was generously supplied by Parke, Davis and Co

In one dog (2-64, figure 12) one adrenal was first removed and the main artery of the kidney on this side was constricted 12 days later. The blood pressure rose significantly, showing the responsiveness of the blood pressure of this animal. At the height of elevation of the blood pressure, the second adrenal was excised and the main renal artery of the corresponding side was permanently constricted. Instead of rising to a higher level, or at least remaining elevated, the blood pressure soon fell to a level below the previous normal for this animal and it died in 11 days of acute adrenal insufficiency.

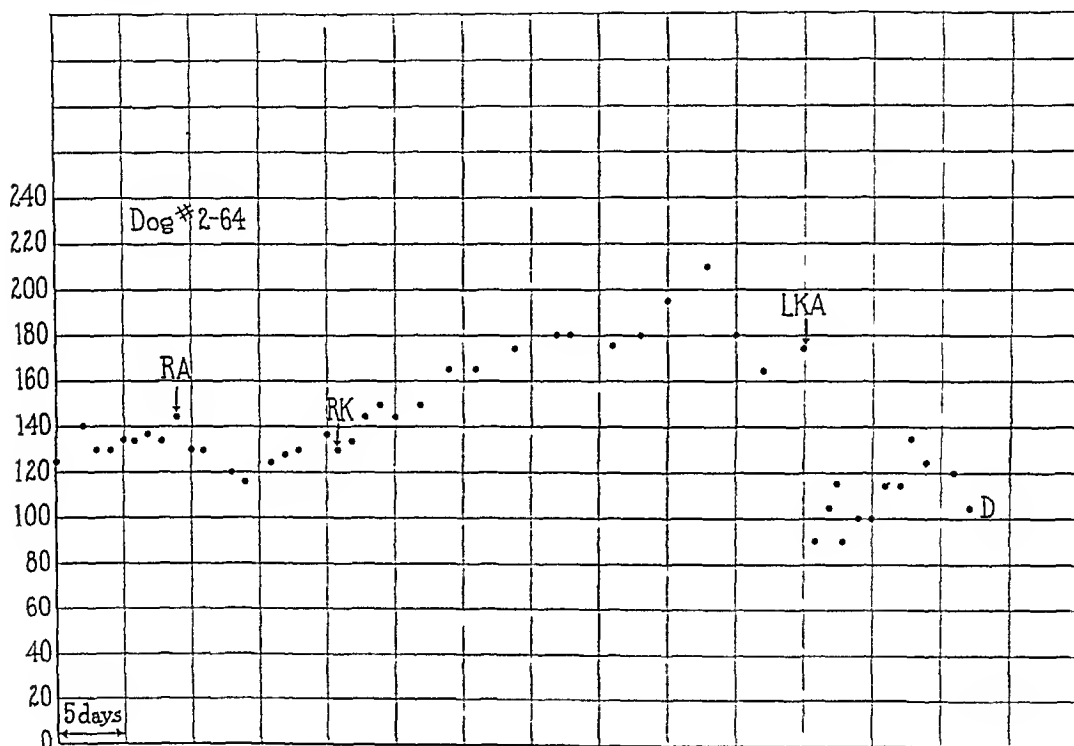


FIGURE 12 Dog 2-64 Female 188 Kg

● = Mean blood pressure, mm Hg RA = Right adrenalectomy RK = Right main renal artery severely constricted The blood pressure became significantly elevated LKA = Left adrenalectomy and left main renal artery moderately constricted The blood pressure fell to below normal level and the animal died of acute adrenal insufficiency D = Died

The results of these experiments show that bilateral adrenalectomy, without supportive or substitution therapy, interferes with the development and maintenance of hypertension which usually follows the production of renal ischemia.

Bilateral Adrenalectomy with Supportive Treatment and Renal Ischemia It has been shown that the life of bilaterally adrenalectomized animals can be prolonged by the administration of sodium chloride¹²¹⁻¹²⁴ or sodium chloride and sodium bicarbonate or sodium citrate¹²⁵

In one dog (2-89 figure 13), the constriction of the main renal artery was carried out on the same side and at the same time as the first adrenalectomy. After this the blood pressure became significantly elevated which demonstrated the responsiveness of the blood pressure of this animal to the effect of renal ischemia. At the end of four weeks, while the blood pressure was still elevated, the second adrenalectomy was removed and the main artery of the kidney on the same side was constricted. Supportive treatment in the form of sodium chloride alone was given by stomach tube during the first 10 days and then sodium bicarbonate was added. After the second adrenalectomy and constriction of both main renal arteries, instead of rising to a higher level, the blood pressure gradually fell to a level below the normal for this animal and death occurred in 19 days.

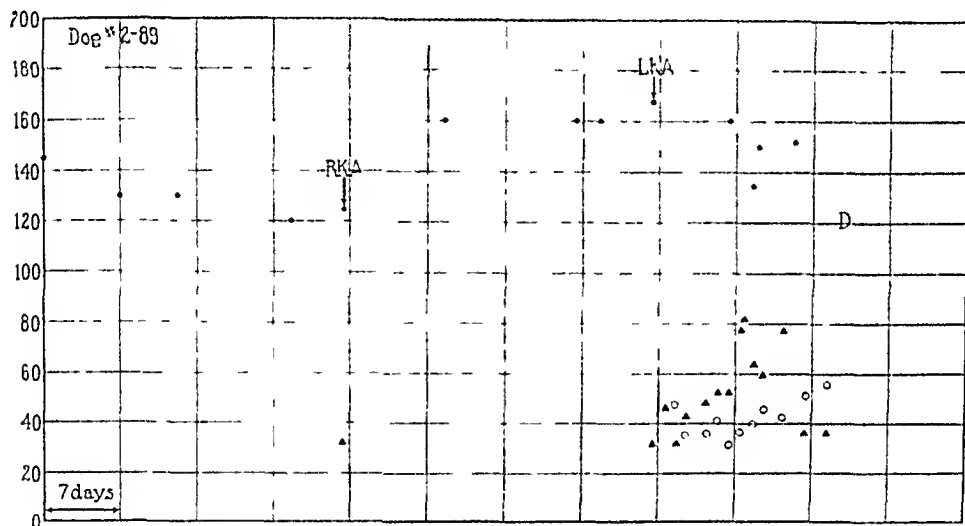


FIGURE 13 Dog 2-89 Male 17.6 Kg

● = Mean blood pressure mm Hg ○ = CO combining power volumes per 100 c.c. plasma ▲ = Non-protein nitrogen mg per 100 c.c. plasma RKA = Right adrenalectomy and right main renal artery moderately constricted. After this the blood pressure showed a moderate elevation LKA = Left adrenalectomy and left main renal artery moderately constricted. From the time of the second adrenalectomy this animal received sodium chloride (0.75 gm per kg of body weight) by stomach tube for 9 days and from then on received in addition sodium bicarbonate (0.25 gm per kg of body weight). There was no greater elevation of blood pressure following the clamping of the second renal artery and the blood pressure gradually fell to below the original level. D = The animal died of acute adrenal insufficiency.

In another dog (2-81) the constriction of both main renal arteries was carried out at the same time as the bilateral adrenalectomy. This was followed by the administration of supportive treatment in the form of sodium chloride and sodium citrate by mouth. The animal survived 15 days but the blood pressure did not become elevated during that period. It fell gradually to a low level and the animal died of acute adrenal insufficiency.

The most convincing proof that in bilaterally adrenalectomized animals supportive treatment alone is not sufficient to permit elevation of blood

pressure or maintenance of elevated blood pressure due to renal ischemia was furnished by four dogs 2-77, 2-87, 2-88 and 3-08 (figures 14 to 17). These animals received both supportive and substitution therapy after the second adrenalectomy but after a varying length of time the administration of cortical extract was discontinued for varying periods. As a result, some of the animals received only supportive treatment in the form of sodium chloride and sodium bicarbonate or sodium citrate by stomach tube for as long as six weeks. In some of these animals the blood pressure remained at the normal or elevated level for a while, but invariably the blood pressure fell to a lower level and rose again to the normal level or higher only when the administration of cortical extract was resumed. These results show that bilateral adrenalectomy, even if followed by supportive treatment, interferes with the development and maintenance of the hypertension which is usually produced by renal ischemia.

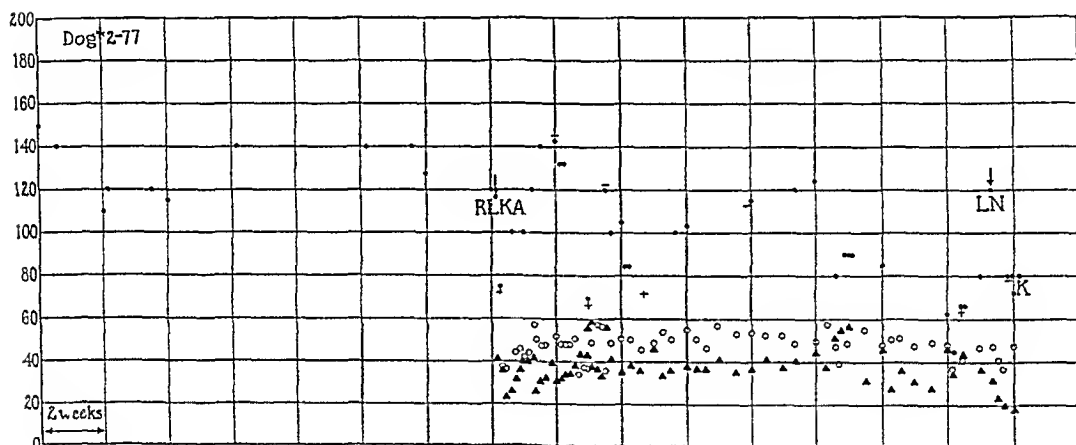


FIGURE 14 Dog 2-77 Female 11.4 Kg

● = Mean blood pressure mm Hg ▲ = Non-protein nitrogen, mg per 100 cc ○ = () combining power, volumes per 100 cc RLKA = Bilateral adrenalectomy and both main renal arteries moderately constricted LN = Left nephrectomy + = Intravenous adrenal cortical extract begun — = Adrenal cortical extract discontinued During the entire period following the bilateral adrenalectomy the animal received by stomach tube in two equal doses (9.00 a.m. and 4.00 p.m.) a total of 0.75 gm per kg of body weight of sodium chloride and 0.25 gm per kg of body weight of sodium bicarbonate. At no time during the four months of survival did the animal show elevated blood pressure. Several times when cortical extract was discontinued, the blood pressure fell to very low levels. K = Killed.

Bilateral Adrenalectomy with Supportive and Substitution Treatment and Renal Ischemia In Dog 2-77 both adrenals were excised and at the same time both main renal arteries were permanently constricted (RLKA in figure 14). During the entire four months of survival following these operations the animal received supportive treatment daily in the form of sodium chloride and sodium bicarbonate by stomach tube and intermittent substitution treatment in the form of intravenous cortical extract. Im-

mediately after the operation the administration of adrenal cortical extract was begun (+, figure 14) At intervals, for varying periods, the administration of cortical extract was discontinued The blood pressure remained at about the normal level during the periods when the cortical extract was also being administered When the cortical extract was discontinued (—, figure 14) the mean blood pressure gradually fell to a low level When the administration of cortical extract was resumed, the blood pressure rose again but never above the normal level This was repeated several times with the same result At no time was the pressure in this animal above normal

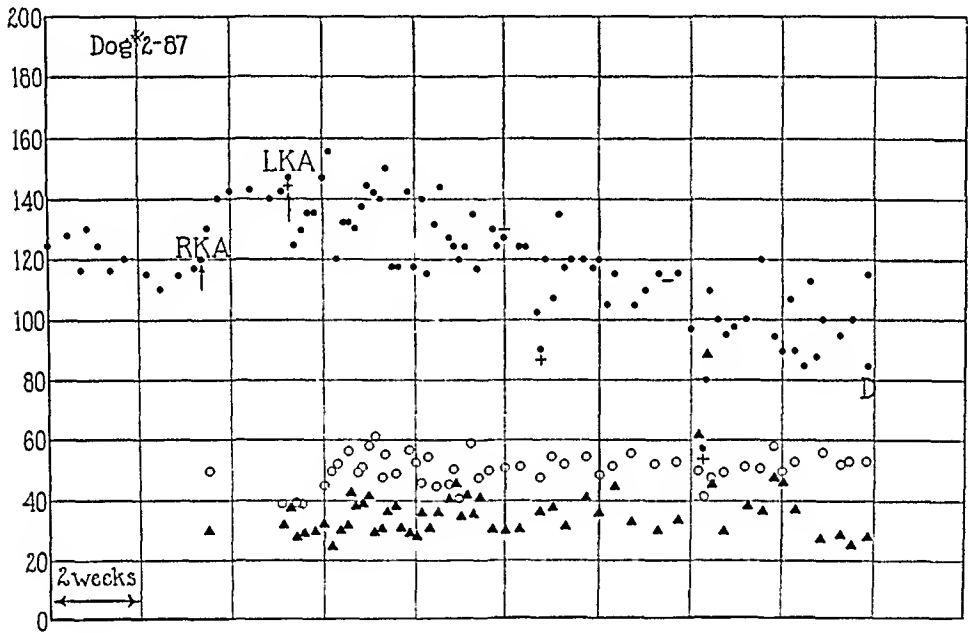


FIGURE 15 Dog 2-87 Female 128 Kg

● = Mean blood pressure, mm Hg ○ = CO₂ combining power, volumes per 100 c c
 ▲ = Non-protein nitrogen, mg per 100 c c + = Intravenous adrenal cortical extract begun
 — = Intravenous adrenal cortical extract discontinued

Sodium chloride (0.75 mg per kg of body weight) and sodium bicarbonate (0.25 gm per kg body weight) were given during the entire period following the second adrenalectomy RKA = Right adrenalectomy and right main renal artery moderately constricted The blood pressure rose moderately LKA = Left adrenalectomy and left main renal artery severely constricted From this time the blood pressure gradually fell to a low level despite the supportive and substitution therapy D = Died

In dog 2-87 (figure 15) unilateral adrenalectomy and constriction of the main renal artery on the same side were first carried out After this first operation no supportive or substitution therapy was given Definite though slight elevation of blood pressure followed this procedure, which demonstrated the responsiveness of the blood pressure of this animal to renal ischemia After the second adrenalectomy and constriction of the corresponding main renal artery, both of which were performed at the

same time, about two weeks after the first adrenalectomy, supportive and substitution treatment were begun. The blood pressure remained elevated for a while but it did not rise to a higher level and, despite the treatment, gradually fell to below the previous normal.

In two dogs (2-88 and 3-08), one adrenal and the kidney on the same side were first removed. After an interval, the second adrenal was removed and the main artery of the only remaining kidney was constricted. During the entire period after the second adrenalectomy, these animals were given supportive treatment in the form of sodium chloride and sodium citrate by stomach tube. Immediately after the second adrenalectomy the administration of intravenous adrenal cortical extract was also begun. At intervals, for varying periods, the administration of cortical extract was

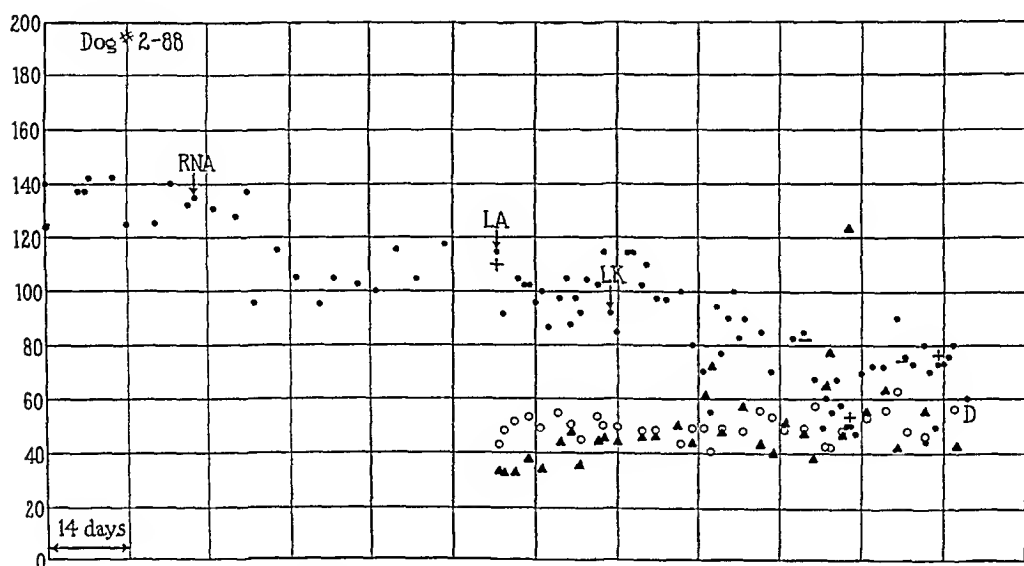


FIGURE 16 Dog 2-88 Female 168 Kg

● = Mean blood pressure, mm Hg ▲ = Blood non-protein nitrogen mg per 100 cc of plasma ○ = CO₂ combining power of blood, volumes per 100 cc of plasma RNA = Right nephrectomy and adrenalectomy LA = Left adrenalectomy LK = Left main renal artery moderately constricted + = Intravenous adrenal cortical extract begun — = Intravenous adrenal cortical extract discontinued

After the left main artery was constricted (LK) the blood pressure gradually fell to a very low level despite the intravenous adrenal cortical extract which was given for long periods at a time and the sodium chloride and sodium citrate which were given by stomach tube twice daily during the entire period following the second adrenalectomy. D = Died

discontinued. In dog 2-88 (figure 16), the main artery of the only remaining kidney was constricted about two weeks after the second adrenalectomy. There was no elevation of mean blood pressure following this procedure but instead the blood pressure fell gradually to a low level despite supportive and substitution therapy. When the cortical extract was discontinued, the blood pressure fell to even a lower level. The animal survived the second adrenalectomy about 12 weeks. During the intervals when cortical extract was discontinued, the mean blood pressure fell to unusually

low levels and rose again, but not even to the original level, when cortical extract was resumed. In the other dog, 3-08 (figure 17) the constriction of the main artery of the remaining kidney was carried out at the time of the second adrenalectomy. Definite elevation of mean blood pressure followed for a period of about one month. During this entire time intravenous adrenal cortical extract was given daily in addition to the salt and

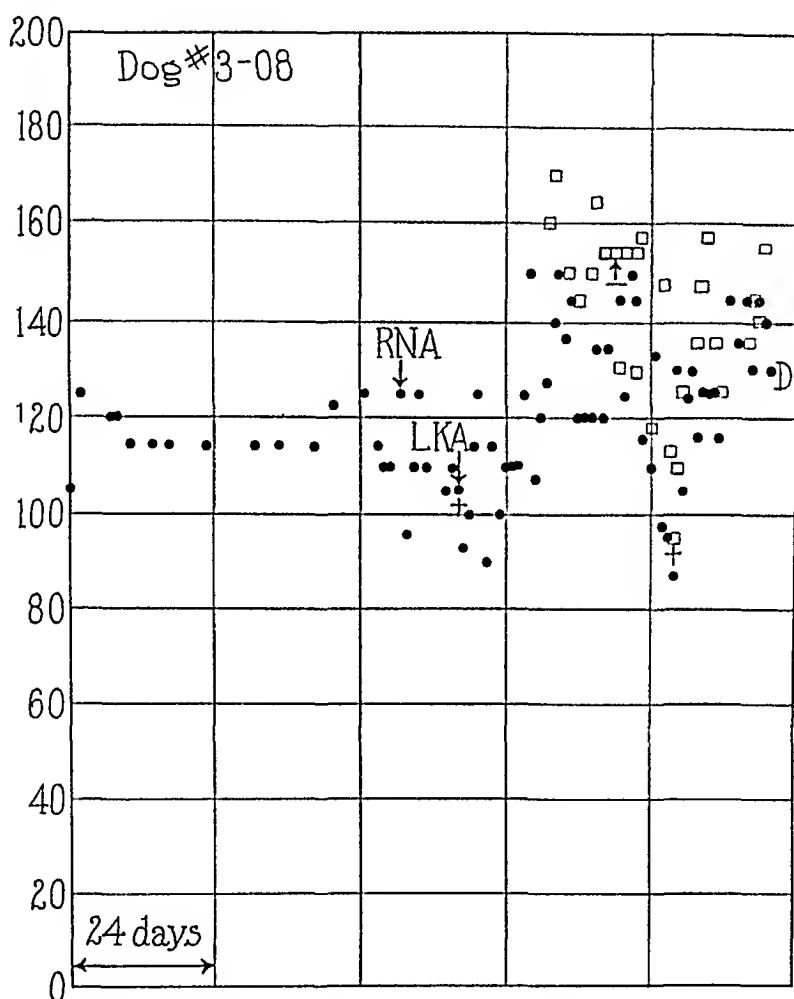


FIGURE 17 Dog 3-08 Female 90 Kg

● = Mean blood pressure, mm Hg. Determinations made in a.m. □ = Mean blood pressure, mm Hg. Determinations made in p.m. 5 hours after the administration of the morning dose of cortical extract, sodium chloride and sodium citrate. RNA = Right adrenalectomy and right nephrectomy. LKA = Left adrenalectomy and left main renal artery severely constricted. + = Intravenous cortical extract begun. — = Intravenous cortical extract discontinued.

Sodium chloride and sodium citrate by stomach tube were given daily during the entire period after the second adrenalectomy.

The blood pressure became moderately elevated and remained elevated for one month during which the dog received substitution as well as supportive treatment. Whenever the intravenous cortical extract was discontinued (—) the blood pressure gradually fell to a level below normal. When cortical extract was begun again (+) the blood pressure gradually rose but did not reach the previous hypertensive level. D = Died of pneumonia.

sodium citrate by stomach tube. When the cortical extract was discontinued at the end of one month, the blood pressure gradually fell to a lower level. When the administration of cortical extract was resumed the blood pressure again became slightly elevated. The animal was accidentally exposed to cold and died of pneumonia.

Up to the present time, definite elevation of blood pressure due to renal ischemia has occurred in one other bilaterally adrenalectomized animal (Dog 2-96) that received substitution and supportive treatment. This animal survived the second adrenalectomy only 19 days. After the constriction of one main renal artery, which was performed eight days after the second adrenalectomy, there was a definite elevation of the blood pressure. Six days later, while the blood pressure was still elevated the main artery of the other kidney was constricted but the animal died the next day.

These results show that, even in the absence of both adrenals, provided adequate substitution and supportive treatment are given some dogs do develop a significant but not great elevation of blood pressure due to renal ischemia. Without substitution treatment such animals do not develop or maintain hypertension due to renal ischemia.

Renal Ischemia in Dogs with No Adrenal Medulla and Only a Small Remnant of Adrenal Cortex. Additional evidence that adrenal cortical hormone is necessary for the development of hypertension due to renal ischemia is provided by the following experiments.

In one dog (3-12 figure 18) approximately three-fifths of one adrenal was excised and the medulla of the remaining portion removed by means of a curette. At this operation the kidney on the same side was removed. At the second operation carried out 19 days later the other adrenal was excised, and the main artery of the only remaining kidney was constricted. In a second dog (3-16 figure 19) exactly the same procedure was carried out but this animal was left with about three-fifths of the cortex alone of one adrenal. There was an interval of 33 days between the two adrenal operations. For a few days following the removal of the second adrenal and constriction of the main renal artery of the only kidney both dogs received supportive treatment in the form of sodium chloride and sodium citrate by stomach tube. No adrenal cortical extract was given at any time. The blood pressure rose promptly following the production of renal ischemia. Even when the supportive treatment was discontinued, the blood pressure remained elevated and in 3-16 rose to even a higher level.

These results are interpreted as indicating the preservation of the function of the small portion of adrenal cortex which was left. In both animals, without the aid of supportive or substitution treatment this small remnant of cortex was sufficient to permit elevation of blood pressure due to renal ischemia. This is additional evidence in support of the view that the hormone of the cortex of the adrenal gland in some way plays a part in the pathogenesis of hypertension due to renal ischemia. More experiments are

being performed in order to elucidate the manner in which this hormone, itself not a vasopressor substance, helps to bring about the pressor effect which follows the production of renal ischemia

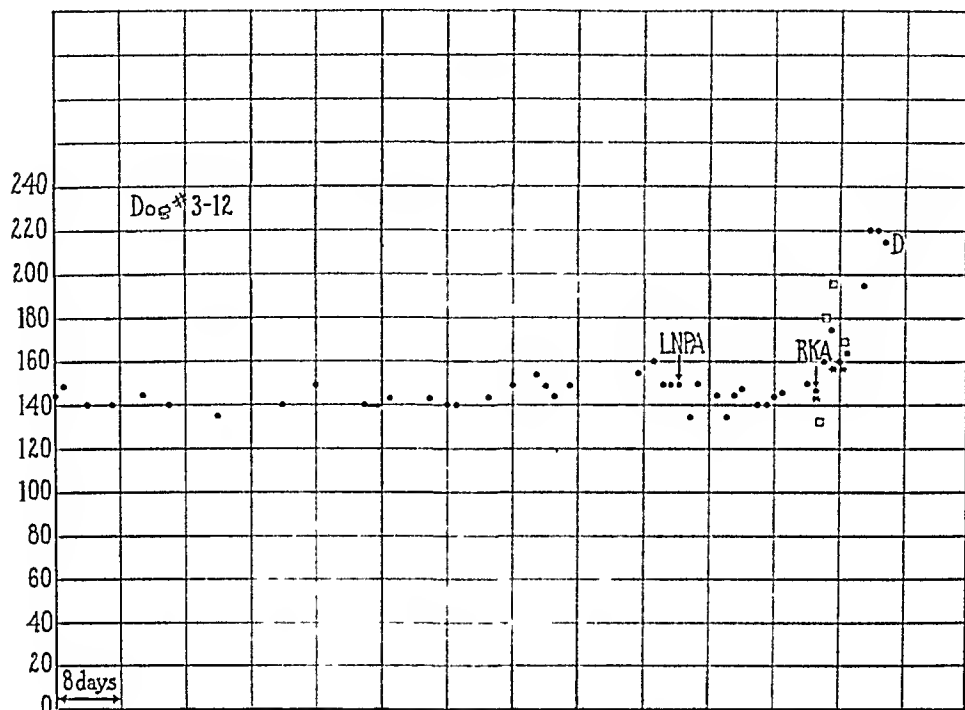


FIGURE 18 Dog 3-12 Female 11.4 Kg

● = Mean blood pressure, mm Hg LNPA = Left nephrectomy and partial adrenalectomy. The medulla was destroyed. About two-fifths of the cortex was left. RKA = Right adrenalectomy and right main renal artery severely constricted. * = Sodium chloride (0.75 gm per kg of body weight) and sodium citrate (0.25 gm per kg of body weight) were given by stomach tube from this time on. ** = Sodium chloride and sodium citrate discontinued. No cortical extract was given at any time. The blood pressure rose moderately following the constriction of the renal artery and remained elevated when supportive treatment was discontinued. D = Died.

SUMMARY

The results of the experiments that have been performed up to the present time on the pathogenesis of hypertension due to renal ischemia indicate that the mechanism of the development of this type of hypertension is primarily a humoral one of renal origin.

The failure of the various surgical procedures carried out on the nervous system to affect this type of experimental hypertension is evidently due to the persistence of the renal ischemia which cannot be altered by these procedures as long as the clamps remain applied. These experiments do not in any way controvert the results that have been obtained by the same procedures in the treatment of hypertension in man. They do emphasize, however, the importance of the reduced blood flow to the functioning

components of the kidney as the primary cause of this type of experimental hypertension and perhaps of human hypertension that is associated with arteriolar disease of the kidneys. Since the reduced blood flow in the human kidney is frequently due to narrowing of the arterioles alone, without narrowing of the large arteries, improvement of the circulation

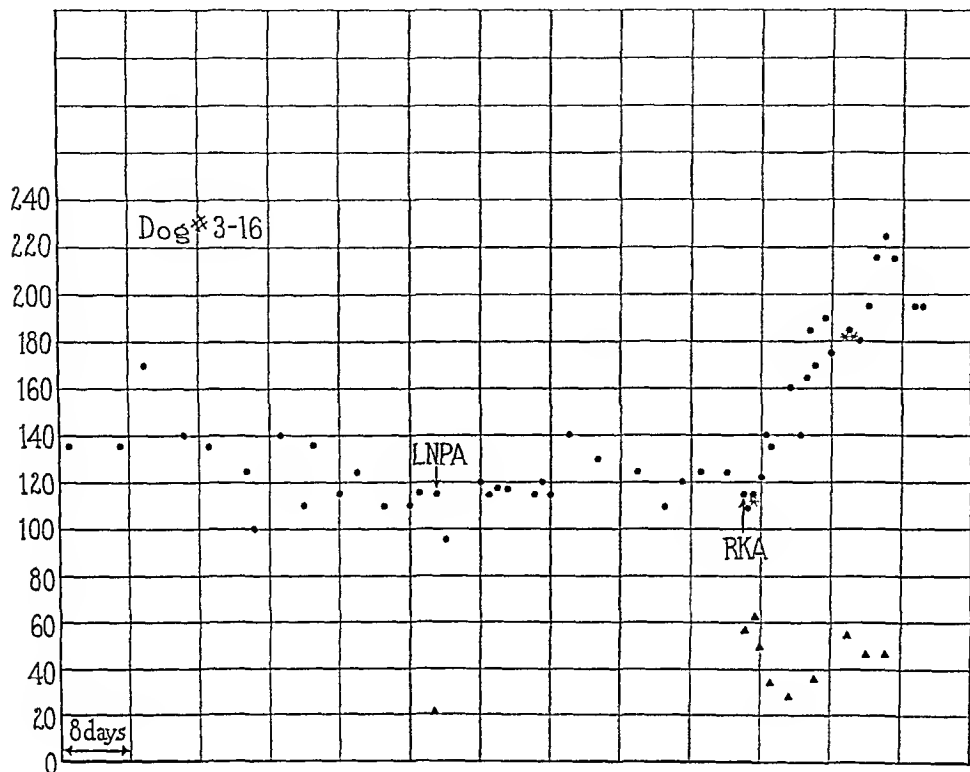


FIGURE 19 Dog 3-16 Female 140 Kg

● = Mean blood pressure, mm Hg ▲ = Non-protein nitrogen, mg per 100 cc plasma LNPA = Left nephrectomy and partial adrenalectomy. The medulla was destroyed. About two-fifths of the cortex was left. RKA = Right adrenalectomy and right main renal artery severely constricted. * = Sodium chloride (0.75 gm per kg of body weight) and sodium citrate (0.25 gm per kg of body weight) were given by stomach tube from this time on. ** = Sodium chloride and sodium citrate discontinued. No cortical extract was given at any time. The blood pressure rose moderately following the constriction of the renal artery and remained elevated when supportive treatment was discontinued. The animal is still living.

may result from these procedures on the nervous system due to relaxation of the arterioles in which the organic changes are not fixed. The beneficial effects reported in about the same percentage of cases of hypertension by surgeons using various procedures affecting the vasomotor nervous mechanism in the abdomen may therefore all be due to one cause, the improvement of the circulation through the kidney and not, as has been suggested by some, to the effect on the vasomotor mechanism of a large part of the vascular bed in the abdomen. The latter view has no support in these experiments. Whether or not improved circulation through the kidney is

responsible for the effect should be put to the test by a large series of renal denervations alone in cases of human hypertension. If improvement of the circulation through the kidneys be the common basis of improvement as a result of all of the various surgical procedures that have been carried out then denervation of the kidneys alone, if it can be accomplished, should give improvement in about the same small percentage of cases of hypertension.

The view that in the pathogenesis of hypertension due to renal ischemia a humoral mechanism involving a hypothetical effective substance of renal origin plays a part of primary importance is based almost entirely upon indirect evidence. Bilateral nephrectomy is not followed by hypertension, yet varying degrees of constriction and even complete occlusion of both main renal arteries are followed by hypertension. This difference is attributed to the absence of a hypothetical effective renal substance when the kidneys are absent. Even when both renal arteries are occluded the hypothetical effective substance can still be formed and washed into the renal veins by the accessory circulation through the capsule. The constriction or occlusion of both main renal arteries when accompanied by occlusion of the main renal veins, is not followed by the development of hypertension. This is interpreted as being due to interference with the entrance of the hypothetical effective substance into the circulation. Release of the constriction of the renal arteries by unscrewing or removing the clamps, causes a prompt return of the blood pressure to normal. The release of the clamp on the main renal artery of only one of two ischemic kidneys is also followed by return of the blood pressure to normal, but it takes longer for the blood pressure to reach the normal than when both clamps are released. This is in keeping with the finding that the clamping of one main renal artery causes only a temporary rise of blood pressure for a varying period. Excision of the ischemic kidney at the height of the hypertension which follows constriction of one main renal artery is also followed by prompt return of the blood pressure to normal. These experiments indicate that if one or two normal kidneys could be transplanted into an animal with hypertension due to renal ischemia, the blood pressure would return to normal because the source of the effective renal substance would be eliminated. Such a study is being carried out at the present time in collaboration with Doctor J. R. Kahn and Doctor W. B. Wartman. Up to the present time the only direct evidence suggestive of the existence of an effective substance has been the demonstration by other investigators^{11, 13} of an increased amount of pressor substance in ischemic kidneys as compared with normal ones.

Various experiments that have been carried out on the effect of complete adrenalectomy, with and without supportive and substitution therapy, and the effect of a small remnant of adrenal cortex only on the prevention or maintenance of hypertension due to renal ischemia indicate that the medulla plays no part, but that the cortex of the adrenal gland may play an important part in the mechanism of development of this type of hypertension.

Complete bilateral adrenalectomy without supportive or substitution therapy interfered with the development of this type of hypertension. Even with supportive treatment, but without substitution therapy, the animals failed to develop or to maintain hypertension due to renal ischemia. In several bilaterally adrenalectomized animals, however, moderate hypertension did develop when adequate supportive and substitution therapy was given. Because of this and because an amount of cortex close to the minimum requisite for survival and even the absence of both adrenals if supplemented by the administration of cortical extract still permitted the development of hypertension due to renal ischemia, the rationale of partial adrenalectomy which has been proposed and practised¹²⁷⁻¹³³ for the treatment of hypertension is questionable to say the least, except in cases of suprarenal tumor¹³⁴⁻¹⁴⁰ with hypertension in which the improvement results from the removal of the tumor in the adrenal.

The exact way in which the adrenal cortical hormone acts in conjunction with the hypothetical effective renal substance in the development and maintenance of hypertension due to renal ischemia has not been elucidated. Although the cortical hormone is not by itself a vasopressor substance, yet it may prepare the arteriolar musculature for the action of the hypothetical effective renal substance, or the reverse may be the case. The two may even combine before exerting their synergistic effect on the arteriolar musculature or they may act in conjunction with other hormones. These various possibilities are now being investigated.

CONCLUSIONS

Persistent hypertension has been produced in animals (dog and monkey) by constricting the main renal arteries which reduces the blood flow to the functioning components of the kidneys (renal ischemia).

Hypertension without or with disturbance of renal function, resembling in this respect the benign and malignant types, respectively, in man, can be produced by varying the degree of constriction of the renal arteries.

The results of various experiments indicate that this type of experimental hypertension is due primarily to a humoral and not to a nervous mechanism initiated by the ischemia of the kidneys.

The nature of the effective substance responsible for inducing the hypertension has not yet been elucidated.

The present indication is that the adrenal cortical hormone plays a part in conjunction with the hypothetical effective substance of renal origin in the pathogenesis of hypertension due to constriction of the main renal arteries.

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THE NATURE OF THE CARDIOVASCULAR DISTURBANCES IN NUTRITIONAL DEFICIENCY STATES (BERIBERI) *

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DURING the past half century significant advances have been made in our knowledge of the etiology of valvular heart disease. Likewise the recognition of the rôle of arterial hypertension, coronary disease, rheumatic myocarditis, adhesive pericarditis, hyperthyroidism, diphtheria and other infectious diseases has enabled clinicians to account for the majority of instances of non-valvular myocardial disease. There remain, nevertheless, a considerable number of patients who present manifestations of myocardial failure without valvular disease or any recognized type of myocardial disease. We have been prone to diagnose such obscure cases as "arteriosclerotic," "coronary" or "hypertensive" heart disease. A rigid scrutiny of evidence, however, including postmortem examination, often fails to corroborate the clinical diagnosis. Hence they remain "idiopathic." These obscure instances of myocardial failure probably include a number of diseases of varied etiology, as yet unrecognized. It is the purpose of this presentation to describe one type of cardiovascular dysfunction heretofore generally unrecognized in this country in which nutritional factors play a causative rôle.

It has been suggested by Shattuck,¹ Wechsler,² Minot, Strauss and Cobb and others that in certain types of polyneuritis a nutritional deficiency and particularly deficiency of vitamin B (B_1) plays an etiological rôle. These studies, however, raised the following question: If alcoholic polyneuritis, polynucuitis of pregnancy and certain other neuritides are related to nutritional deficiencies, and particularly deficiency of vitamin B_1 , why are they not associated with other manifestations, namely cardiovascular dysfunction such as occurs in patients with beriberi in other parts of the world? Soon after this question was raised we encountered in our wards two patients with nutritional deficiency polyneuritis, who suffered in addition from a severe degree of "idiopathic" circulatory failure. We therefore undertook a study of (a) the clinical characteristics of this condition, (b) the

* Presented in part before the St. Louis meeting of the American College of Physicians, April 19, 1937.

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This investigation was aided by grants from the Proctor Fund of Harvard University for the Study of Chronic Disease and the Josiah Macy, Jr. Foundation.

physiological, chemical and morphological changes, (c) the etiology, and (d) therapeutic measures. A summary of the first part of this investigation was presented before the 1936 meeting of the Association of American Physicians.⁴

MATERIAL AND METHOD OF STUDY

In order to determine whether the disease exists as a clinical problem, we undertook an analysis of the records of some 900 patients suffering from various types of nutritional deficiency, including general malnutrition, chronic alcoholism with or without polyneuritis, pellagra, neuritis of pregnancy and diabetes. In this group we discovered 85 cases in which cardiovascular dysfunction of varying severity could not be ascribed to the usual etiological factors. Because all instances in which organic lesions of the cardiovascular system existed were eliminated and because many of the cases were observed by physicians not experienced in cardiovascular problems, the number selected must be considered as minimal. This conclusion is corroborated by the fact that within a period of two years we have personally studied 35 patients from a total of 5,506 admissions to two general medical services in this hospital. The observations here presented are therefore based on a total group of 120 cases.

OBSERVATIONS

Nature and Pathogenesis of Cardiovascular Dysfunctions

Age and Sex Incidence The ages of the 120 patients varied between 24 and 67 years, 84 per cent fell in the age group 30 to 59 years. Eighty-two per cent were males and 18 per cent females. This age and sex incidence can, however, be considered but an approximation, since the majority of the cases have been gathered from available records and numerous elderly patients were eliminated because of the simultaneous presence of hypertension or arteriosclerosis.

Nutritional History The majority of the patients were heavy consumers of alcohol. A smaller group gave a history of unbalanced diet as a result of psychic peculiarities ("food cranks"), of drug addiction or medical restriction of diet or of persistent nausea, such as is present in pregnancy. In relatively few patients poverty played a rôle. The caloric intake was adequate or more than adequate in the majority, as was also indicated by their weight. Reliable detailed history was obtainable in only a small group. The estimated vitamin B (B_1) intake in this group was less than that indicated by Cowgill as liable to produce polyneuritis. There were a few patients, on the other hand, in whom both the caloric and the estimated vitamin B (B_1) intake were adequate. In this group there were usually indications of digestive dysfunction suggesting lack of proper absorption or utilization of the essential food substances.

Symptoms and Signs of Non-Cardiovascular Origin Cardiovascular

abnormalities were present in the majority of instances, along with other recognized manifestations of nutritional deficiency and particularly with those of "beriberi" and pellagra. In a smaller group scurvy was present. In some instances, however, circulatory failure was the sole manifestation. Table 1 shows the associated signs not referable to the cardiovascular system. In a given patient one or more of these signs were present in various combinations, but peripheral neuritis, gastrointestinal disturbances and psychosis were most frequent.

TABLE I
Non-Circulatory Manifestations

Peripheral neuritis	Hypoproteinemina
Psychosis	Optic neuritis
Glossitis	Dysphagia
Constipation	Hoarseness
Diarrhea	Aphonia
Dermatitis	"Spoonied" nails
Anemia	Purpura

Symptoms and Signs Referable to the Cardiovascular System. The clinical symptoms and signs referable to the cardiovascular system are presented in table 2. The most frequent combinations of symptoms and signs

TABLE II
Circulatory Manifestations

<i>Symptoms</i>	
Tachycardia with palpitation	Prominent cardiac pulsation
Fatigability	Pulmonary rales
Dyspnea on exertion	Engorged veins
Cough	Gallop rhythm
Edema	Warm extremities
Orthopnea	"Pistol" sounds
Paroxysmal dyspnea	Dilated heart
	Cyanosis
<i>Signs</i>	Syncope
Tachycardia	Circulatory collapse
Embryocardia	Bronchopneumonia
Systolic murmurs	Diastolic murmurs

were dyspnea on exertion with tachycardia and embryocardia, palpitation with gallop rhythm, prominent cardiac and epigastric pulsations, bounding peripheral pulses with sounds ("pistol shots"), particularly over the carotid, subclavian and femoral arteries, and edema, both diffuse and dependent, with distended veins. The skin was often flushed and warm. In 24 patients selected for special study, the cardiovascular disturbance was severe and, at times, extreme.

The *heart* was normal in size or enlarged. There was usually a prominent precardial pulsation with a rapid systolic rise and diastolic fall. At times the extensive thoracic pulsations over the heart suggested cardiac enlargement, but this was not always corroborated by roentgenological examination. The heart rate was usually rapid. Under rest and dietary

treatment the tachycardia returned to the normal level, either slowly or rapidly. In the latter case transient bradycardia frequently followed.

The character of *dyspnea* varied considerably. In the majority of patients dyspnea occurred only on slight or moderate exertion. In some, continuous dyspnea and orthopnea developed. Several patients without evidence of pulmonary infection complained of an irritating, dry "hacking" cough, particularly annoying at night. Patients with typical attacks of cardiac asthma (paroxysmal dyspnea) were also encountered. In some instances attacks of dyspnea appeared with unexpected suddenness in patients who had been in vigorous health. Such attacks were also observed in bed-ridden patients. Signs of pulmonary congestion were frequently present, and cloudiness of the lung fields was seen on roentgenological examination. Patients with severe polyneuritis were less liable to have advanced failure of the circulation. The most plausible explanation for the infrequent coexistence of the two conditions seems to be that the polyneuritis prevents muscular exertion.

The *arterial pressure* was usually normal with a tendency to increased pulse pressure. In some cases the systolic pressure was moderately elevated during the acute stage of circulatory failure, but it returned to normal when the patient's condition had improved. The *venous pressure* was elevated or normal.

Edema was present in one group of patients. In some it was of extreme degree and diffuse, in others only dependent in type. Often at the time of admission the severity and extent of edema were not appreciated. A patient with full, round facies and robust appearance rapidly changed to a thin-faced individual with a delicate bodily structure. Decreases in the osmotic pressure of the blood, even when present, could not be held responsible because the edema often disappeared while the osmotic pressure remained essentially unchanged. The protein content of the edema fluid was low (Cases 1, 2 and 4).

Attacks of *syncope* were observed in five patients. The attacks were associated with asystole and fall in the arterial pressure, and they could be induced by stimulation of the carotid sinus. The hyperactive carotid sinus reflex in these patients was of the vagotonic type. Following the administration of a diet rich in vitamin B (B_1), the irritable state of the carotid sinus reflex subsided and in four cases stimulation of the sinus subsequently produced no symptoms and no asystole. The fifth patient developed an acute psychosis and was transferred to another institution.

Circulatory collapse developed in some of the patients with congestive failure of the circulation. In other instances in which it occurred the only premonitory sign was tachycardia.

Patients with severe congestive failure of the circulation were especially prone to develop *fever*. The condition of these patients often became much more serious with the onset of an elevated temperature. In some cases the

fever seemed to have precipitated the congestive failure. It is equally plausible, however, that the reverse was true. Signs of bronchopneumonia were often detected, but sometimes the cause of fever remained obscure even after postmortem examination.

Electrocardiographic Studies. Electrocardiograms taken in 67 cases with normal blood pressures and with no clinical evidence of organic heart disease disclosed abnormalities in all but five cases (table 3). Figures 8

TABLE III
Electrocardiographic Findings in 67 Cases

	No. of Cases	% of Total
Normal records	5	7
Abnormal records	62	93
Change in direction of T-wave	46	68
Stimulus tachycardia (100 or over)	42	63
Prolonged Q-T (electrical systole)		
Above Echer-Li standards (Upper limit of K-Miles 0.38 females 0.42)	53	79
Above Shipley-Hillman standards (Upper limit of K-Miles 0.43 females 0.45)	30	45
Ventricular premature beats	10	15
Auricular premature beats	9	13
Low voltage of QRS (below 5 mm.)	6	9
Auricular fibrillation	3	4
Intraventricular block	3	4

11, 12, and 15 are examples of the electrocardiographic changes observed. These changes occurred in patients with nutritional deficiency or with clinical polyneuropathy, pellagra, psychosis, or combinations of these syndromes. In some instances no other clinical manifestations of deficiency disease existed. Not all patients with the same type of nutritional deficiency had changes in the electrocardiograms; nor were they present in all instances of polyneuropathy or pellagra. No explanation can be offered for their absence in patients with apparently the same underlying disease. The electrocardiographic changes disappeared with improvement after the administration of a diet rich in vitamin B or of crystalline vitamin B₁. Patients were also observed in whom the abnormality of the electrocardiogram appeared or became accentuated immediately after administration of vitamin B₁ or of food rich in vitamin B (B₁), only to disappear eventually.

Hemodynamics of the Circulation. In 13 patients technical measurements of the circulation were made. The velocity of the blood flow, the oxygen difference of the blood in the femoral artery and vein, the vital capacity of the lungs and the venous pressure in the antecubital and femoral veins were usually measured on several occasions. The most significant finding was that patients with enlarged heart, rapid heart rate, gallop rhythm, dyspnea, orthopnea, generalized edema, low vital capacity and elevated venous pressure had a normal or increased velocity of blood flow and a low arteriovenous oxygen difference. Such behavior of the circulation differs from that in other types of organic heart disease in which there

generally exists a direct relationship between the degree of congestive failure and the slowing of the blood flow^{5, 6}

The rapid blood flow confirmed the clinical impression created by the warm extremities, the flushed color, the bounding pulses and the increased arterial pulse pressure namely, that there was a *generalized arteriolar dilatation*. This is an important factor in the clinical picture. Indeed after treatment with vitamin B₁ one of the most constant and dramatic effects was the slowing of the circulation to a normal or temporarily even to a sub-normal level. The beneficial effect in lowering peripheral capillary pressure and thereby enhancing the removal of edema fluid by the venules was demonstrated in several patients who had diuresis following this slowing while the osmotic pressure of the blood and the venous pressure remained unchanged (Cases 2, 3 and 4). Arteriolar constriction following B₁ therapy must also react, in turn, centrally on the heart in the same beneficial manner as the closing of an arteriovenous aneurysm.

With improvement after vitamin B₁ therapy the heart rate slows, the gallop rhythm subsides and the size of the heart returns to normal. The elevated venous pressure falls, the vital capacity increases and the edema, orthopnea and dyspnea disappear. A simultaneous study of the heart, peripheral vascular system and circulation indicates that the failure of the circulation in patients with nutritional deficiency depends on the combined effects of dilatation of the peripheral arteriolar system and myocardial failure.

While some of the patients exhibited the syndrome of pure *right ventricular failure*, this was not the characteristic manifestation. There were generally symptoms and signs of *left ventricular failure* as well. Moreover patients with only pulmonary congestion and edema, exhibiting attacks of paroxysmal dyspnea, were also observed. In some patients rapidly developing *circulatory collapse* or shock dominated the clinical picture. Our observations therefore fail to reveal a rigid circulatory syndrome. In general the clinical picture in patients with a severe degree of circulatory failure was characterized by (a) good and often rapid peripheral circulation associated with warm skin, high bounding pulse with arterial sounds and normal or increased velocity of blood flow, (b) a failing heart with preponderant right or left ventricular failure, as indicated by high peripheral venous pressure and edema, or by dyspnea, orthopnea, paroxysmal attacks of dyspnea associated with low vital capacity, the physical signs of congestion, and cloudiness of the lung fields in the roentgenogram, (c) a tendency to terminal circulatory collapse or shock.

Chemical Changes. Analysis of the blood chemistry revealed the following trends: (1) Moderate lowering of serum proteins and colloid osmotic pressure, (2) normal or moderately increased non-protein nitrogen, (3) moderate elevation of fasting blood sugar, (4) normal carbon dioxide capacity, (5) increase in bisulphite binding substances⁸. The urine analyses showed tendency to ketosis, and occasional glycosuria.

Organic Heart Disease and Nutritional Deficiency

An especial attempt was made to study cardiac and circulatory disturbances in relation to nutritional deficiencies in their pure form. Whether nutritional factors play a rôle in patients with organic cardiovascular disease was not the main interest of the investigation. This problem is particularly difficult because of the two simultaneously existing major variables and because no objective index is available for measuring the specific relationship of circulatory failure to nutritional deficiency. We have encountered patients with hypertensive and chronic rheumatic heart disease, however, in whom a severe degree of congestive failure has been precipitated on repeated occasions by lack of proper food or by the consumption of large amounts of alcohol.

Frequency

The cardiovascular disturbances here described occurred in a ratio of about 1 in 160 admissions to the medical wards. A comparison of the occurrence of this type of cardiovascular dysfunction with the frequency of some of the other diseases of the cardiovascular system indicates that in this hospital the condition is more frequent than congenital heart disease, adhesive pericarditis, hyper- or hypothyroid heart disease and subacute bacterial endocarditis. The relative frequency of the condition, however, will vary considerably in different strata of society, in different races and in various parts of the country.

Prognosis

Under proper medical management the condition offers a good prognosis in the majority of instances. In the advanced stage, particularly if the deficiency has existed for a long time, the circulatory failure may terminate fatally in spite of treatment. Among the 35 cases personally observed, fatalities due to acute failure of the circulation occurred in four, two of which were untreated. In an additional five cases death was due primarily to other causes. The improvement may be rapid or slow. The determining factors in the rate of improvement have not been established, but the duration as well as the severity of the nutritional deficiency seems to be important. Final recovery is apparently complete in those patients who survive the acute failure.

Differential Diagnosis

The absence of the recognized etiological causes of organic heart disease, on the one hand, and the history of unbalanced diet or digestive dysfunction, on the other, should suggest the possibility that the cardiovascular disturbance is of nutritional origin. If certain non-circulatory manifestations of vitamin deficiency described above are also present, such a possibility is enhanced. The combined presence of congestive failure of the circulation and a relatively or absolutely increased rate of the circulation makes the

diagnosis probable The assured diagnosis depends on complete recovery of the patient in response to rest, and to diet or extracts rich in vitamin B₁. Some cases of obscure myocarditis may offer difficult differential diagnostic problems The history of unbalanced diet and of the peripheral vascular signs are of aid in such problems

Treatment

As in other types of heart disease, evaluation of the efficacy of therapeutic measures is difficult, mainly because of the inadequacy of control observations Patients with circulatory failure caused by nutritional deficiency kept at rest in bed, with or without digitalis, diuretics and other measures, usually showed a moderate degree of improvement In three cases, however, severe circulatory embarrassment with collapse indicated the possible harmful effects of such a control period In 25 patients observed during the past 12 months the usual method of study was as follows On entrance to the hospital the patient was kept in bed and was given a special diet deficient in "B" vitamins Usually no medication was given or occasionally digitalis and diuretics were administered in relatively large doses during a period of from four to seven days Frequent measurements of various functions of the circulation were made Following these control observations, all medication was discontinued and vitamin B₁ extract, or, more recently, crystalline vitamin B₁ was administered intravenously, intramuscularly or subcutaneously several times a day for from four to seven days* During this period the vitamin "B" deficient diet was continued and the measurements and clinical observations were repeated Subsequently the parenteral administration of vitamin B₁ was replaced by a diet and oral extracts rich in vitamin B₁ The dosage of crystalline vitamin B₁ varied In the early stage of our studies we used doses of 10 to 20 mg a day More recently we have given an average of 50 mg and as high as 130 mg a day Because there is but scant available information on the elimination and storage of vitamin B₁ in the human body, the dosage is necessarily empirical We have purposely administered considerably larger doses than those indicated by animal experiments"

In spite of the fluctuation of the state of the circulation during the control period, following the administration of extracts or crystals of vitamin B₁, as indicated by the illustrative cases, the improvement was frequently striking In general the improvement was most rapid in patients with a severe degree of congestive failure The first change observed was the increased utilization of oxygen and slowing of the blood flow, which occurred in eight cases in which measurements were made within 24 hours following the administration of the first dose of vitamin B₁ These initial

* Two preparations were used for parenteral administration a highly purified and standardized preparation of vitamin B₁, obtained through the courtesy of the Winthrop Chemical Company, Inc., New York, and crystalline vitamin B₁, obtained through the courtesy of Merck & Company, Inc., Rahway, New Jersey

changes in the circulation, accompanied by subjective improvement, were followed by a marked degree of diuresis, slowing of the heart rate and decrease in the venous pressure. Simultaneously there was a slow but steady rise in the vital capacity of the lungs and a decrease in cardiac size. The cardiovascular abnormalities last to disappear were those revealed by the electrocardiogram. No untoward symptoms were observed even after such a large intravenous dose of crystalline B_1 as 50 mg. In some patients a temporary elevation of the arterial pressure of several days' duration followed the first course of treatment.

Although our primary interest was the study of cardiovascular dysfunction in relation to nutritional deficiencies, we have had opportunity to observe the response of patients with *polyneuritis* to crystalline vitamin B_1 . There was no parallelism between the rate of improvement in the circulatory functions and in the nervous functions. The improvement usually was more striking, rapid and complete in the cardiovascular than in the neurological disturbances. The latter, particularly when chronic, in spite of the large doses of crystalline vitamin B_1 , returned only slowly and incompletely toward normal. In a few instances, on the other hand, particularly in the mild cases of short duration, improvement in vibration sense, paresthesias and motor function occurred within two days after treatment was instituted.

Effect of Crystalline Vitamin B_1 on the Non-Deficient Cardiovascular System

Seven patients with no vitamin deficiency were given parenteral crystalline vitamin B_1 in doses ranging from 10 to 120 mg. a day for from one to seven days. In no case was there significant change in any aspect of the heart or of the circulation. In two patients, shortly after injection there occurred temporary minor changes in the electrocardiograms. Four patients had edema on which the vitamin had no diuretic effect. Two patients with clinical signs of B_1 deficiency (*polyneuritis*) but without cardiovascular dysfunction showed no changes in the heart or circulation following large doses of crystalline B_1 . Two patients who initially had had vitamin deficiency and cardiovascular dysfunction of the type described, which returned to normal after the first course of B_1 , showed no effect when a second course of vitamin was given several weeks later (Cases 3 and 4).

Morphological Observations

Wenckebach¹⁰ has described microscopical changes in the hearts of patients with "beriberi heart" in Java, which he has claimed are characteristic, if not specific. We have therefore examined sections of the hearts of patients who died as a result of alcoholic and other types of nutritional *polyneuritis* or *pellagra*, with or without the type of cardiovascular disturbances described above. Of 30 cases 19 exhibited cardiovascular dysfunction in addition to tachycardia. Death in these cases was often the

result of sudden circulatory collapse, associated with terminal bronchopneumonia. The myocardial fibers and the conductive bundle of this group exhibited various degrees of "hydropic" degeneration. In addition, intercellular edema and collagen were present. Figures 1, 2, 3, 5, 6, and 7

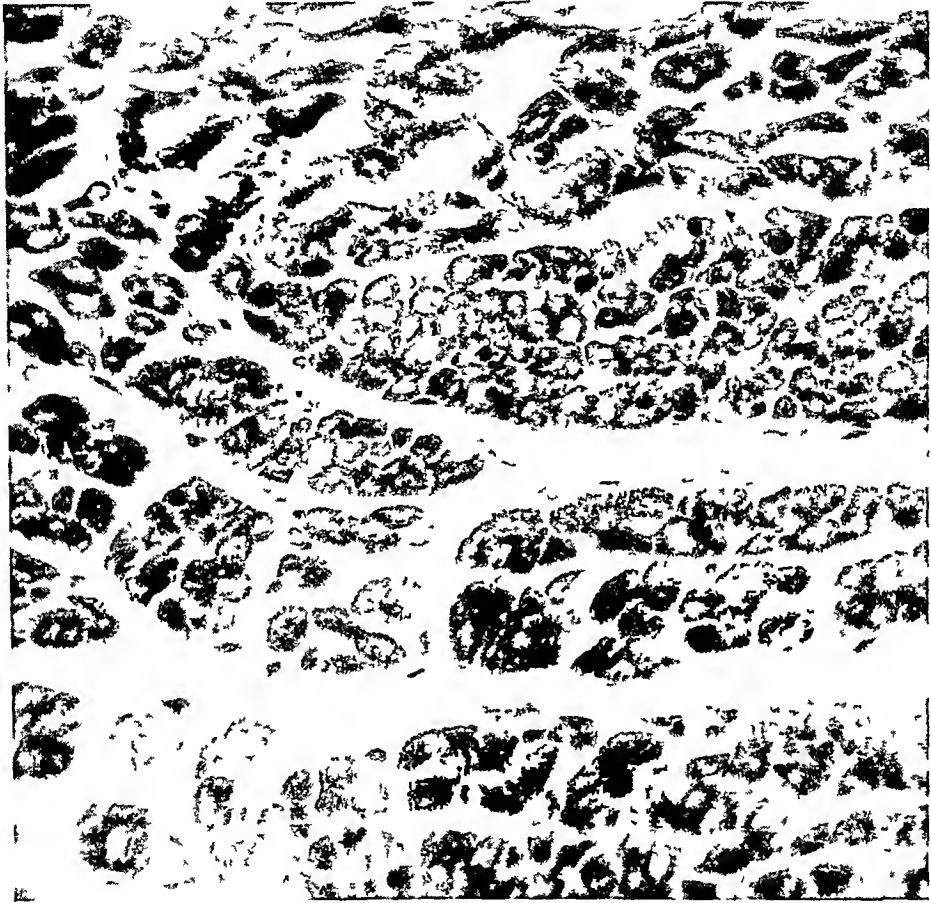


FIG 1 "Hydropic" degeneration of muscle fibers of the heart with "interstitial edema" in pellagra and polyneuritis 400 X

demonstrate the types of changes observed. No relationship could be found between the degree of histological change and the clinical manifestations. In no instance was there evidence of inflammation.

The sections of the hearts of the group with nutritional deficiency and cardiac failure, as well as of cases with polyneuritis or pellagra without heart failure, have been compared with cardiac sections of two control groups. The first group consisted of eight cases of portal cirrhosis of the liver without manifestations of vitamin deficiency. The second group included 14 cases without heart disease and four cases with fatal organic heart disease. In both control groups there were cases with a moderate degree of "hydropic" degeneration and with interstitial edema similar to that found in the deficient group.

The size of the heart varied. In the majority of instances the weight of the heart was normal, and there was moderate dilatation of the right ventricle. In nine out of 30 cases there was an increase in weight and a considerable degree of dilatation of the cardiac chambers, particularly the right ventricle. In the group observed by us dilatation of the right ventricle

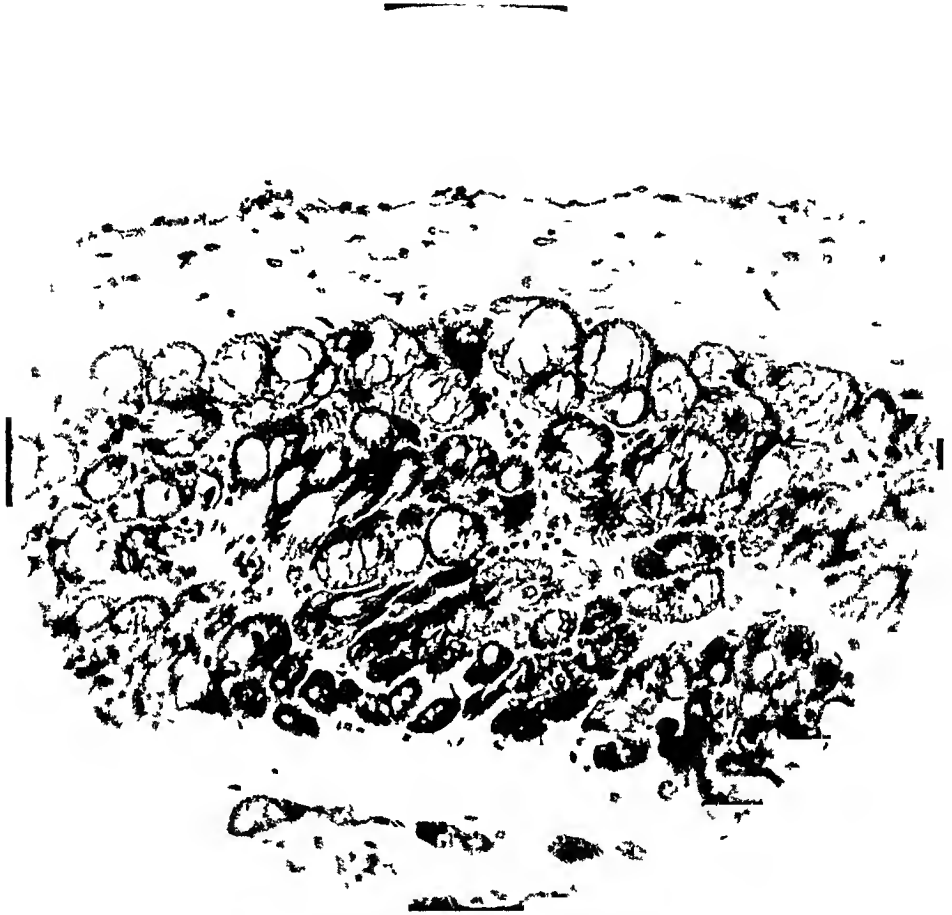


FIG. 2 "Hydropic" degeneration of cross sections of subendocardial conductive fibers in pellagra and polynneuritis. 200 X

was not as marked or as frequent as in the group of "beriberi hearts" studied by Wenckebach in Java.¹⁰ The histological changes, on the other hand, were identical with those described by Wenckebach. Our data, in contrast to those presented by Wenckebach, do not indicate that the histological changes observed are specific or even characteristic. They can be present in other diseases.

Sections of the brain revealed swelling of the ganglion cells with marginal displacement of cell nuclei within the vagus centers. In one case there was destruction of the cells with replacement by glia nodules (Dr. L. Alexander).

Water Content of Cardiac and Skeletal Muscles

Aalsmeer and Wenckebach¹¹ have suggested that deficiency of vitamin "B" produces physicochemical and physiological alterations in the body which lead to water retention in the cardiac and skeletal muscles. They

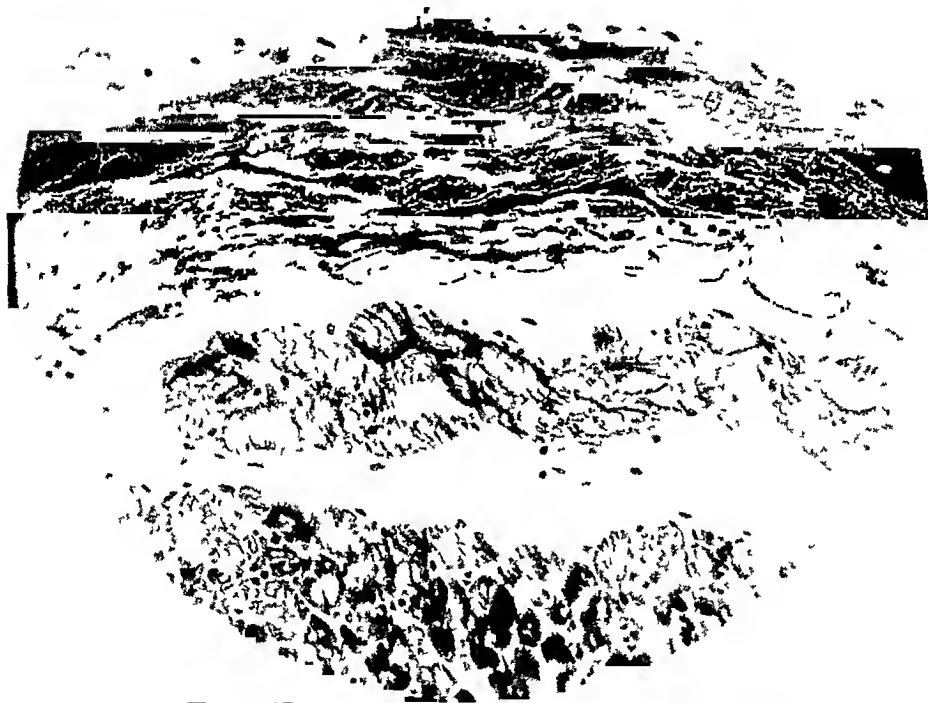


FIG 3 "Hydropic" degeneration of longitudinal section of subendocardial conductive fibers in pellagra and polyneuritis

have claimed that the "hydropic" degeneration and interstitial edema are indications of such changes. Wassermeyer¹² reported that the heart of birds deficient in vitamin B contains more water than that of normal animals.

In order to obtain information on this phase of the problem, we have measured the water content of the right and left ventricles and of the abdominal rectus muscle in the following conditions: (a) nutritional deficiencies with or without heart failure, (b) control group with no heart disease, (c) organic heart disease with anasarca.⁴ The water content was measured with a gravimetric method. The group with nutritional deficiencies included three patients with combined polyneuritis and pellagra, one

with scurvy and polyneuritis and five with nutritional deficiency, heart failure and cardiac dilatation. No significant difference in the water content of the heart in various groups was observed. It is of interest that even in the group with organic heart disease and with generalized anasarca and with low serum protein, the water content of the myocardium

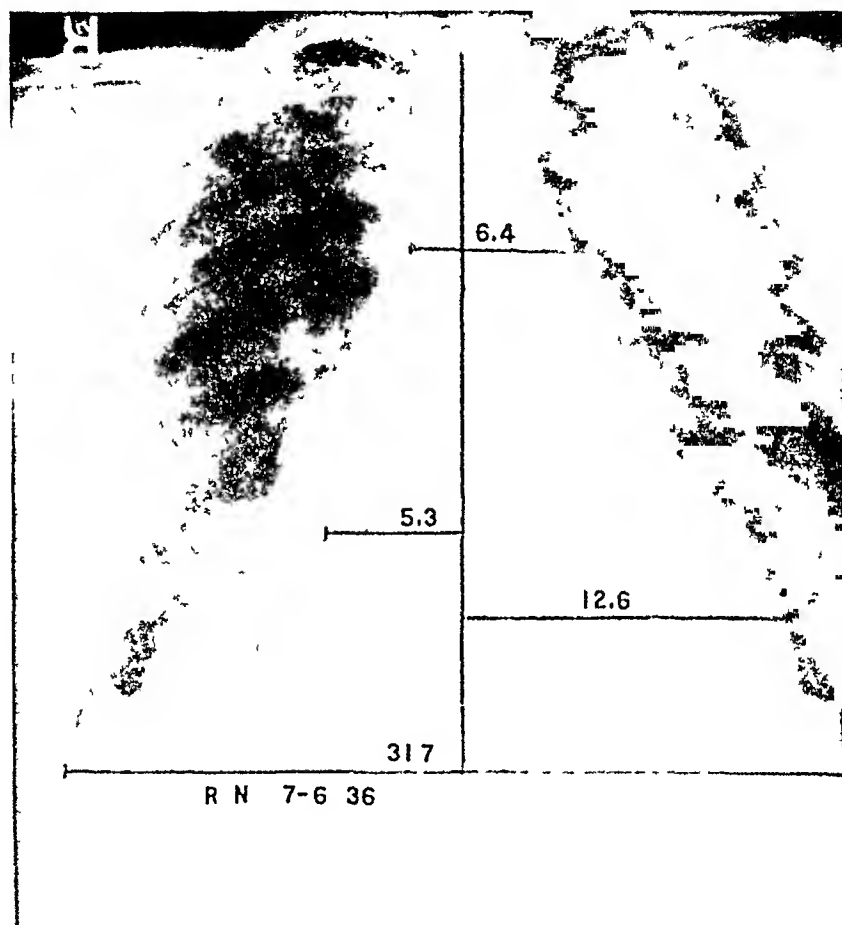


FIG 4 The cardiac shadow in Case 1

remained essentially normal. The abdominal rectus muscle, on the other hand, showed at times increased water content in the presence of anasarca.

Case Reports Illustrating Types of Cardiovascular Disturbances and Therapeutic Responses Observed

The following cases are reported in detail as examples of the types of cardiovascular disturbances encountered and of the responses to the therapeutic agents administered. Additional cases have been reported in a previous communication.⁴

Case 1 *Severe congestive failure of the circulation, mild pellagra and polyneuritis, fatal circulatory collapse* R N, an odd-job man, aged 36 years, had been drinking $\frac{1}{2}$ pint of alcohol daily for two years, and one pint to one quart a day for three months. He had eaten a grossly inadequate diet which became more deficient the more he drank. He complained of increasing dyspnea on exertion for one month, dependent edema for three weeks, hacking cough for 10 days and orthopnea with insomnia for one day.

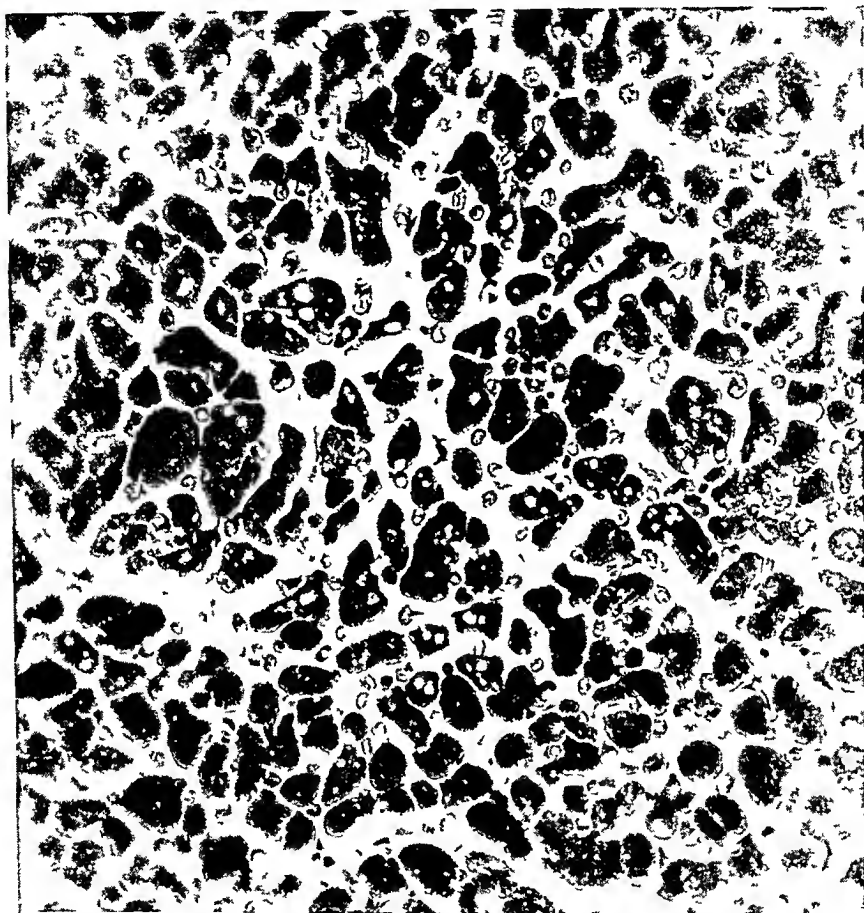


FIG 5 "Hydropic" degeneration of the muscle fibers in Case 1

The family history and past history were non-contributory.

Physical examination revealed a well-nourished, slightly jaundiced man with severe orthopnea and diffuse edema, more pronounced in the dependent parts. There was pigmentation and scaliness of the skin on the dorsum of the hands and feet and on the lower legs. The veins of the neck were engorged. The heart was percussed 12 cm to the left and 5 cm to the right of the midsternal line. A gallop was heard at the apex and a blowing systolic murmur at the base of the heart. The second sound at the pulmonic area was accentuated. The heart rate was 120 per minute and the rhythm was regular, arterial pressure 110 mm Hg systolic and 46 diastolic. "Pistol" sounds were audible over the carotid and femoral arteries. The lower third of both lungs posteriorly was dull to percussion, and over these areas and also anteriorly over the left hilar region moist râles were heard. The abdomen was pro-

tuberant and there was shifting dullness in the flanks. A firm liver edge was palpable 4 cm below the right costal margin. The spleen was not felt. Knee jerks were greatly diminished and ankle jerks were absent. Temperature 98° F. Respirations 36 per minute. Weight 183 pounds (usual weight 160 pounds).

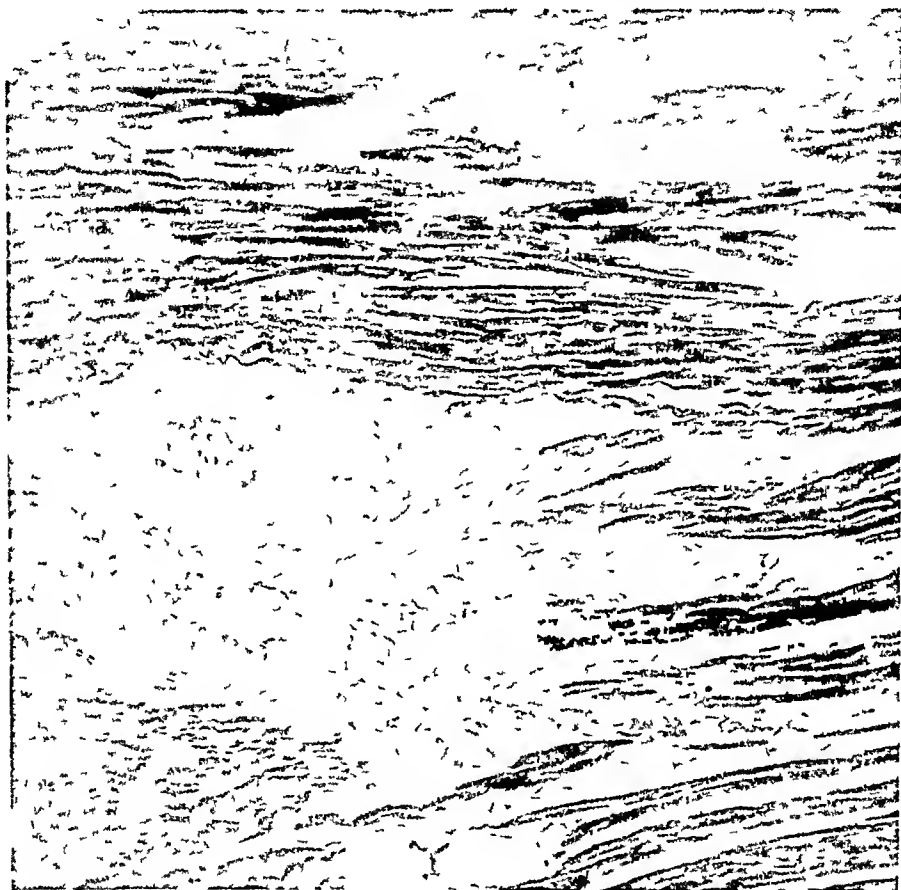


FIG 6 Perivascular "edema" and separation of the muscle fibers in Case 1

Laboratory studies *Urine*, acid, specific gravity 1.025, albumin trace, sugar 0 bile positive, sediment, occasional leukocytes and hyaline casts. *Blood*, hemoglobin 87 per cent, erythrocytes 4,430,000 per cu mm. Icterus index 14. Total protein content of the plasma 5.2 gm per 100 cc, albumin 2.92 gm and globulin 2.28 gm, with calculated osmotic pressure 200 mm H₂O. The non-protein nitrogen of the plasma was 65.6 mg per 100 cc. The Hinton test was positive. The Takata-Ara test was negative. *Edema fluid* from the thigh contained total protein 1.50 gm per 100 cc, albumin 1.10 gm and globulin 0.40 gm.

A 7-foot roentgenogram of the heart confirmed the clinical measurements (figure 4). The electrocardiogram was interpreted as within normal limits except for tachycardia. Special circulatory studies showed the venous pressure in the femoral and cubital veins to be 27 cm H₂O, the circulation time 15.5 seconds, the femoral arteriovenous oxygen difference 0.75 volumes per cent, and the brachial arteriovenous oxygen difference 1.39 volumes per cent. The vital capacity was 2,500 cc.

While this patient obviously was suffering from severe circulatory failure with rapid blood flow, he was made fairly comfortable with small doses of morphia. It

was thought safe to withhold therapy until a control period had elapsed. There was subjective relief, but there were no changes in the edema or other signs of circulatory failure. On the third day the venous pressure had risen to 32 cm H₂O. It was then decided to give vitamin B₁, but before it could be administered the patient suddenly went into circulatory collapse, from which he died.

Postmortem examination revealed marked anasarca and mild jaundice of all tissues. The heart weighed 520 gm. The right auricle and ventricle showed marked dilatation and moderate hypertrophy, the left auricle and ventricle were normal. Except for the aortic cusps, at the bases of which were minimal atheromatous thicken-



FIG 7 Separation of the muscle fibers by edematous collagen in Case 1

ings, all valve cusps were thin, membranous and translucent. There was no evidence of rheumatic or luetic endocarditis. The coronary arteries, the epicardium and the pericardium were normal. The aorta showed minimal atheromatous change $\frac{1}{2}$ cm above the aortic valve, but otherwise was perfectly normal.

The right lung weighed 1,300 gm and the left 1,080 gm. The pleural surfaces were smooth and glistening, but purple in hue. There were slight depressed scars at each apex. The crepitation was markedly decreased, giving the lungs a "meaty" consistency. The cut surfaces were uniformly purplish-red throughout all lobes of both lungs. There was an extreme degree of edema and congestion, and large quantities of serosanguineous fluid could be easily expressed. In the base of the right lower lobe was one small area of minimal bronchopneumonic consolidation.

The liver weighed 2,480 gm. It was firm, the surface smooth, its capsule thin and of normal translucence. Its entire surface showed a marked "nutmeg" appearance. The kidneys, spleen and other abdominal viscera were markedly congested.

The brain weighed 1,560 gm. There was atrophy of both frontal lobes, most pronounced in the pre- and post-central gyri. There were several very small petechial hemorrhages in Ammon's horn. The spinal cord and peripheral nerves were normal in appearance. The rest of the gross examination was normal.

Microscopy revealed these additional findings. The right ventricle showed marked "edema" of the intermyocardial connective tissue, with separation of the muscle fibers. There was also "intracellular edema" of the myocardium (figures 5, 6, and 7). The left ventricle showed marked increase in the collagenous connective tissue of the epicardium. There was an increase in the interstitial tissue, especially that lying immediately beneath the epicardium. This connective tissue was extremely "edematous," causing separation of the myocardial cells.

The lungs showed marked dilatation and congestion of the capillaries of the alveolar walls. The alveoli contained many large macrophages filled with brown pigment, many extravasated erythrocytes and granular debris. In one area numerous polymorphonuclear leukocytes were present.

The liver showed extreme fatty degeneration. Many cells, especially in the centers of the lobules, were degenerated. There was no increase in connective tissue. No "alcoholic" hyaline was seen. The brain showed widespread perivascular hemorrhages and degenerative changes in numerous pyramidal cells.

Case 2 Congestive failure of the circulation, polyneuritis, Korsakoff's psychosis, improvement on vitamin B₁. W. E., an unemployed painter aged 50 years, was disoriented and confused and gave an unreliable history. He admitted taking one pint of pure alcohol daily for years and stated that he rarely ate anything. He was brought in by welfare workers from a cellar where he had been living for weeks, unable to move. He had no complaints.

Physical examination revealed an extremely weak, poorly nourished man with diffuse edema which involved the sternum and face. He lay flat in bed in no apparent distress. The skin of the face showed marked acne rosacea with crusted pustular lesions. The skin of the extremities was dry, scaly and very warm. There was a pustular conjunctivitis and a small white ulcerous plaque on the right cornea. The pupils were quite small and reacted sluggishly to light. The tongue was smooth on the edges. There was moderate engorgement of the veins of the neck. The heart was percussed 11 cm. to the left and 6 cm. to the right of the midsternal line. The sounds were of poor quality but there were no murmurs. The heart rate was 90 per minute and the rhythm was regular. The arterial pressure was 105 mm. Hg systolic and 75 diastolic. Sounds were audible over the carotid, femoral and brachial arteries. The lungs were resonant, but moist rales were heard over the lower third of both lungs posteriorly. In the abdomen the liver edge was felt 1 cm. below the right costal margin. There was bilateral wrist- and foot-drop. The biceps and triceps jerks were greatly diminished and the knee and ankle jerks were not obtainable. There was marked muscle and nerve tenderness in the legs. Sensory examination was unsatisfactory, but there was apparently hypesthesia of the lower legs. Temperature was 99° F. Respirations 25 per minute. Weight 158 pounds.

Laboratory studies. *Urine*, acid, specific gravity 1.012, albumin 2 plus, sugar 0, bile 0, acetone 0, diacetic acid 0, pyruvic acid 0, sediment, many leukocytes and hyaline casts. *Blood*, hemoglobin 74 per cent, erythrocytes 3,200,000 per cu. mm., leukocytes 9,150, neutrophils 78 per cent. The fasting blood sugar was 144.5 mg. per 100 c.c. and the non-protein nitrogen 98 mg. The total protein content of the plasma was 5.3 gm. per 100 c.c., albumin 3.0 gm., globulin 2.3 gm., with calculated osmotic pressure 207 mm. H₂O. The icterus index was 10. The Hinton test was negative. The Takata-

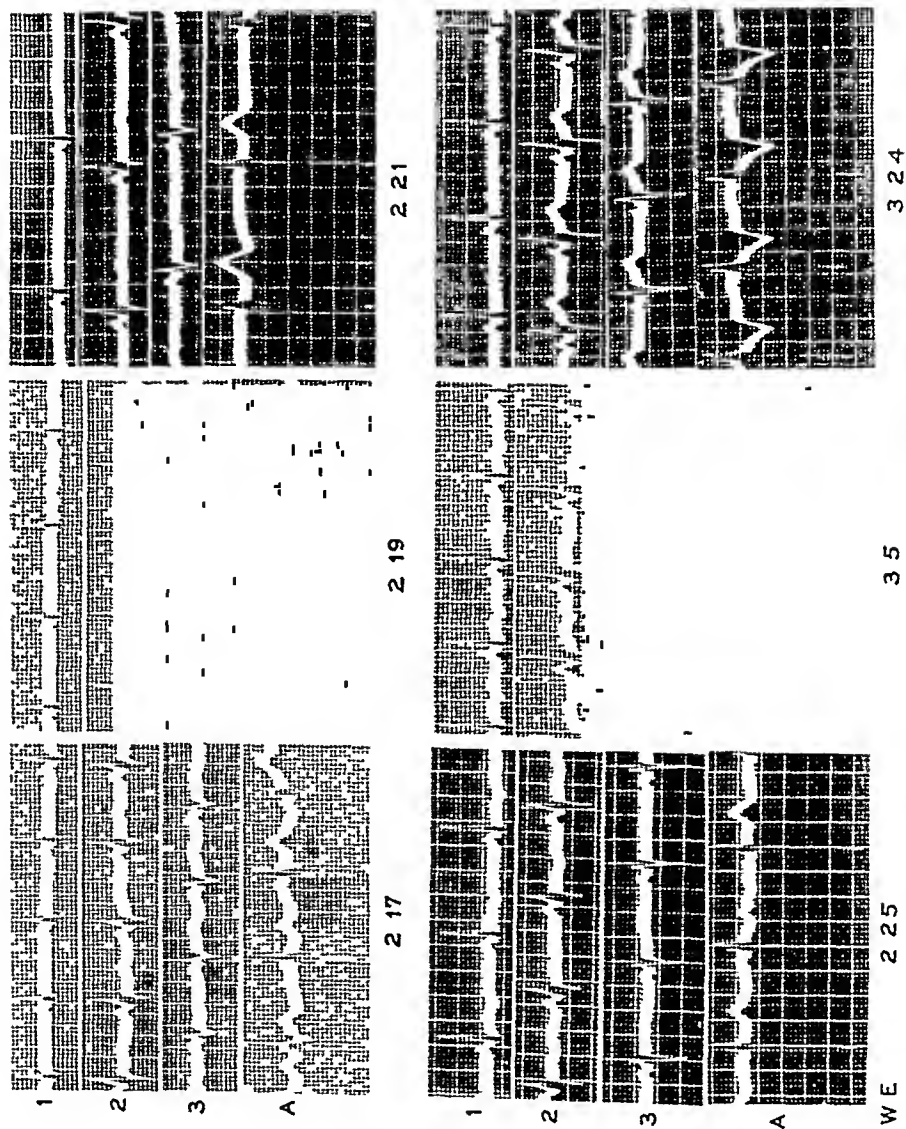


FIG 8 Electrocardiograms in Case 2 Note changes in amplitude and in T-waves

Aia test was positive. The bisulphite binding substances in the blood were 9.9 mg per 100 cc (as pyruvic acid). Edema fluid from the arms showed a total protein content of 1.2 gm per 100 cc, albumin 0.66 gm, globulin 0.55 gm. Lumbar puncture revealed a spinal fluid pressure of 200 mm H₂O, normal dynamics and a normal fluid.

Special circulatory studies showed vital capacity 1,700 cc, venous pressure 17 cm H₂O, circulation time 11 seconds and femoral arteriovenous oxygen difference 1.84 volumes per cent. The electrocardiogram (figure 8) showed low voltage (7 mv), abnormal T-waves and prolonged Q-T interval (K equals 0.47) interpreted as myocardial disease. The 7-foot roentgenogram confirmed the enlargement of the heart found clinically (figure 9).

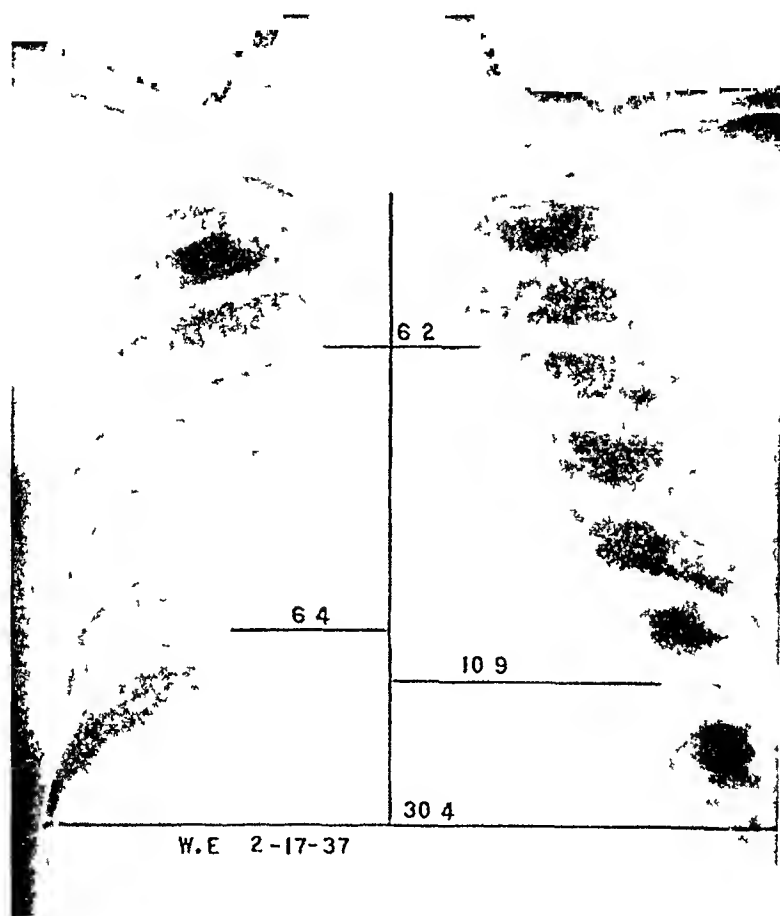


FIG 9 The cardiac shadow in Case 2 before treatment

The patient was placed on a vitamin-free diet, fluids ad lib, no other therapy. His course is graphically shown in chart 1. On the second day it was found that he had retention of urine, necessitating constant drainage. On the fourth day he lapsed into coma and appeared moribund. There had been no essential change in any aspect of the circulation or blood chemistry. It was decided not to delay vitamin therapy. Accordingly, 30 mg of synthetic crystalline vitamin B₁ were administered intravenously. At that time the patient was in deep coma, had Kussmaul breathing, and extremely small pupils which did not react to light. One hour and a half after the injection there was a most remarkable change. The patient aroused, asked for water,

then took a large bowl of boiled milk and crackers. The breathing became normal, the pupils were dilated and reacted normally to light and on accommodation. Vitamin B₁ was continued, both intravenously and subcutaneously, in large doses. In this case it seemed to have been life saving.

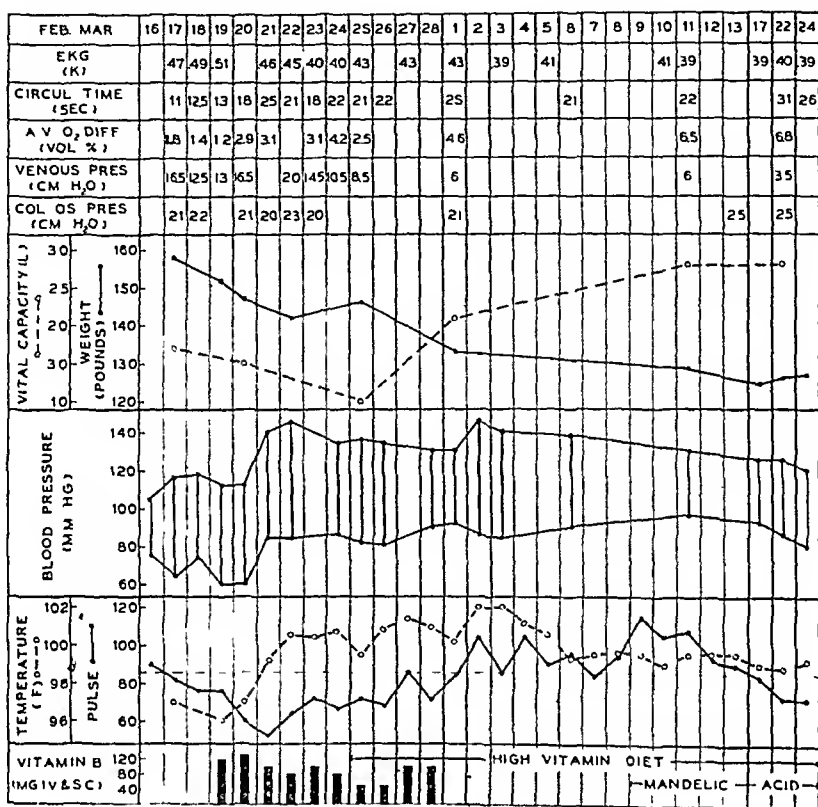


CHART 1 The clinical course in Case 2

The next day the heart rate was 60 per minute, the circulation time 18 seconds, and the femoral arteriovenous oxygen difference 29 volumes per cent. The arterial pressure, venous pressure and colloid osmotic pressure of the blood were unchanged. On the second day after vitamin B₁ therapy was instituted the heart rate was as low as 52, the arterial pressure was 140 mm Hg systolic and 84 diastolic and the electrocardiogram (figure 8) showed increased voltage (10 mv). The circulation time was 25 seconds and the arteriovenous oxygen difference 31 volumes per cent. The slowing of the circulation shown by these measurements was all the more remarkable in view of the fact that the patient now had a fever due to cystitis and also, probably, to bronchopneumonia. The latter diagnosis could not be established because, while there were signs of dullness, bronchovesicular breathing and moist râles over the hilar regions of both lungs posteriorly, these signs might have been due simply to increased pulmonary congestion resulting from compensation of the right ventricle out of proportion to the left. We have observed these signs without fever in similar cases, and in this case the fever continued after the lungs had cleared and until the urinary infection was brought under control. The vital capacity decreased during this period, but later returned toward normal. On the third day of vitamin therapy the non-protein nitrogen, the bisulphite binding substances in the blood and the Q-T interval of the electrocardiogram were within normal limits. There was still no

change in the venous pressure or the colloid osmotic pressure of the blood. Clinically, in spite of the fever, the extremities were now cool, the sounds had disappeared over the brachial arteries and were barely audible over the femoral arteries. There was less edema, especially of the upper part of the body.

This patient's course was complicated by a prolonged febrile episode, due to the stubborn cystitis which required forcing of fluids. Nevertheless, he responded well to the vitamin therapy. On the sixth day of this treatment the edema had greatly decreased and the venous pressure was normal. The colloid osmotic pressure of the blood was still unchanged. He was then placed on a high vitamin diet, and after four days the parenteral vitamin B₁ was discontinued.

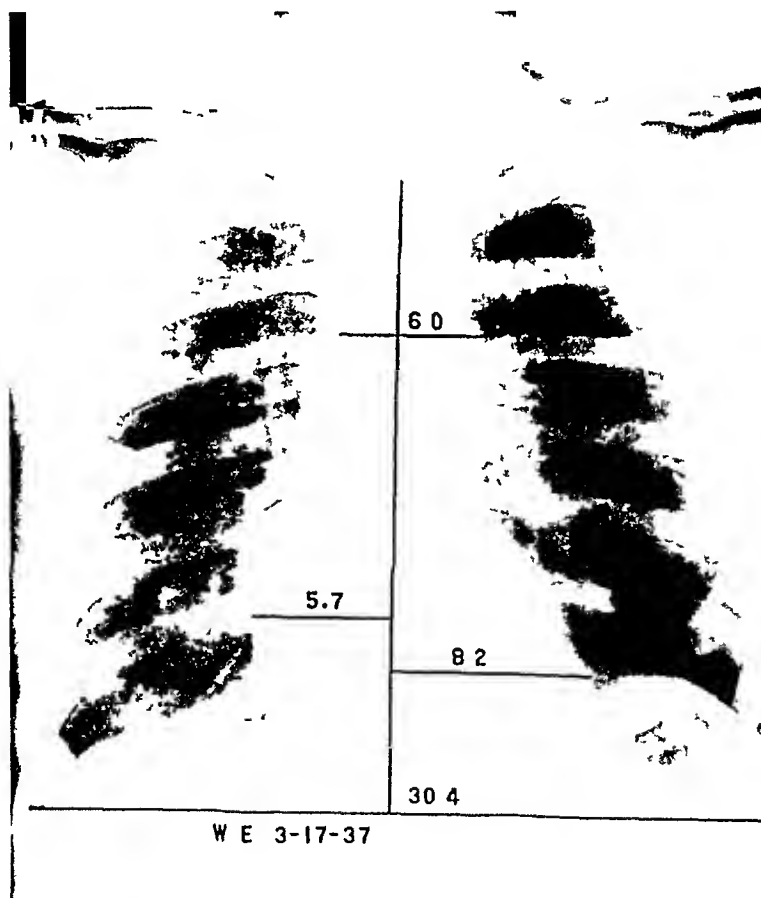


FIG 10 The cardiac shadow in Case 2 after treatment

Convalescence was steady and complete. The patient regained voluntary control of his bladder and the cystitis was relieved by mandelic acid. One month after admission a 7-foot roentgenogram showed that the heart had decreased to normal size (figure 10). Except for a flat T-wave in the first lead, the electrocardiogram was normal (figure 8). The vital capacity was 2,800 c.c. The patient had lost a total of 34 pounds. In the fifth week the knee jerks returned, and the strength was greatly improved. During the sixth week the patient was up and about the ward. He began to gain weight without edema. The protein content of the blood plasma was normal. Mentally, although greatly improved, he was still defective. His memory was poor and he confabulated. Consequently, at the end of the sixth week he was committed to a sanatorium for chronic care.

Case 3 *Congestive failure of the circulation and polyneuritis, improvement after vitamin B₁ therapy* J S, a laborer, aged 36 years, had drunk $\frac{1}{2}$ to 1 pint of whisky and many glasses of beer daily for 15 years. His food intake had been scanty, and particularly deficient in vitamins. He complained of palpitation on exertion for three months, of dependent edema for one month, which had involved the scrotum for one day, and of dyspnea on exertion for three weeks.

The family history was non-contributory. The past history was negative except for one previous hospital admission two years before, for alcoholic gastritis.

Physical examination revealed a well-nourished, nervous man fairly comfortable in bed, with marked edema of the scrotum and slight edema over the shins and sacrum. The color was quite florid and the skin was warm and moist. The heart was percussed 12 cm to the left and 5 cm to the right of the midsternal line. The sounds were tic-tac in quality and there was a short blowing systolic murmur at the apex. The heart

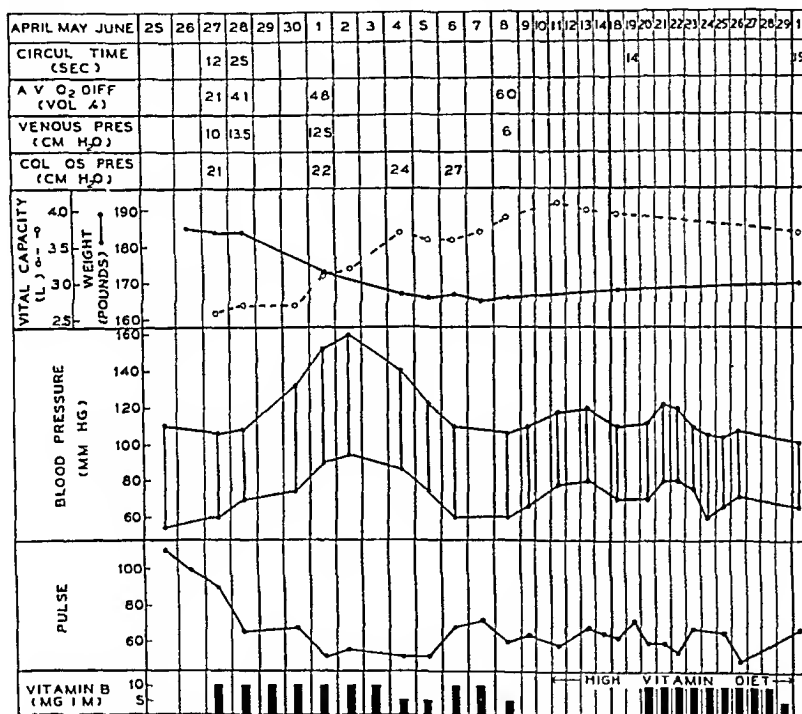


CHART 2 The clinical course in Case 3. Note the temporary elevation of the arterial pressure following the first, but not the second course of crystalline vitamin B₁.

rate was 110 per minute and the rhythm was regular. The arterial pressure was 110 mm Hg systolic and 54 diastolic. Systolic sounds were audible over the carotid, femoral and brachial arteries. The lungs were resonant and clear except for moist rales at the left base posteriorly. The abdomen was negative. The knee jerks and ankle jerks were not obtainable. Temperature 99.2° F. Respirations 24 per minute. Weight 185 pounds.

Laboratory studies. *Urine*, alkaline, specific gravity 1.020, albumin, sugar, bile and sediment negative. *Blood*, hemoglobin 90 per cent, erythrocytes 4,260,000 per cu mm, leukocytes 4,700, neutrophils 61 per cent. The non-protein nitrogen was 32 mg per 100 cc. The Kahn test was negative. The Takata-Ara test was negative. The basal metabolic rate was plus 4 per cent.

This patient was not seriously ill on admission, indeed, aside from the swelling of the scrotum there was no striking evidence of circulatory failure. He was placed on a low vitamin diet and all medication was withheld. On the third day there was no change clinically. Studies on that day showed the following: weight 185 pounds, arterial pressure 106 mm Hg systolic and 60 diastolic, heart rate 90 per minute, vital

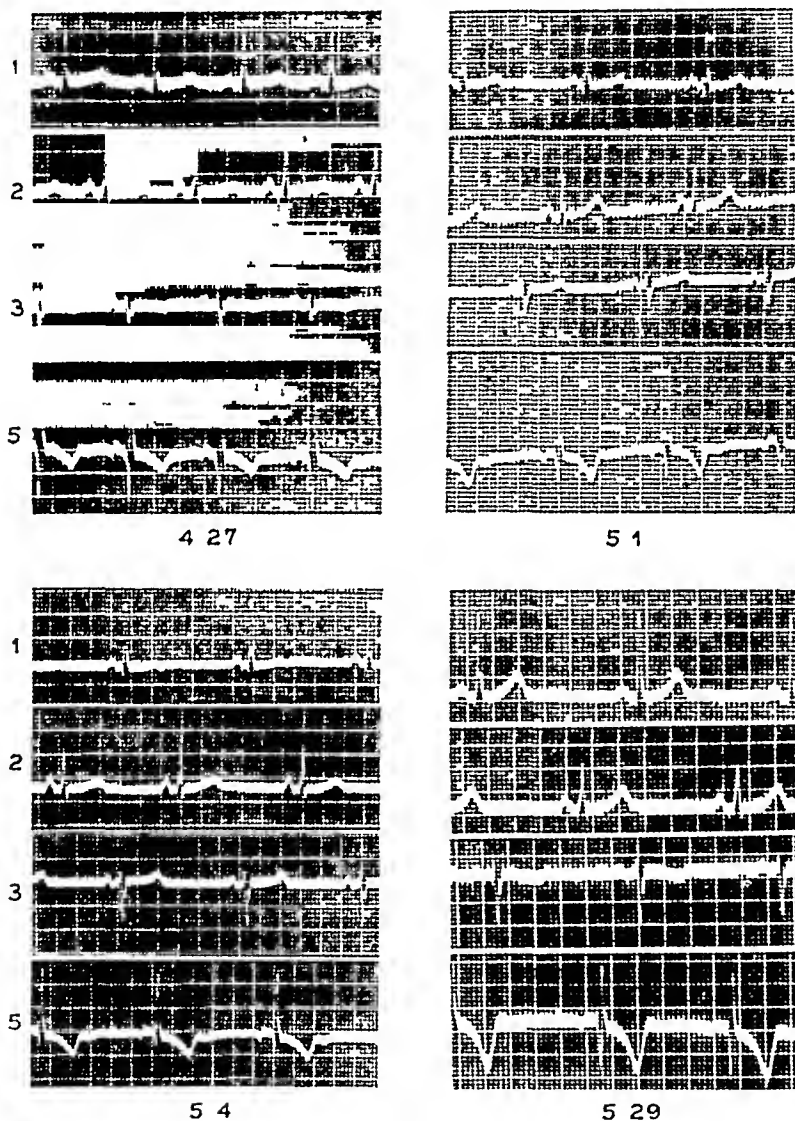


FIG 11 Electrocardiograms in Case 3. Note changes in T-waves.

capacity 2,600 c.c., venous pressure 10 cm. H₂O, circulation time 12 seconds, the femoral arteriovenous oxygen difference 20.8 volumes per cent. The total protein content of the blood plasma was 5.07 gm. per 100 c.c., the albumin 3.28 gm. and globulin 1.79 gm., with a calculated osmotic pressure of 210 mm. H₂O. The electrocardiogram showed no abnormality (figure 11). A 7-foot roentgenogram of the heart showed the heart enlarged as observed clinically.

After these observations vitamin B₁ was given intramuscularly in 5 mg doses twice daily. The clinical course and circulatory measurements are shown in chart 2. The striking changes one day after the vitamin were the slowing of the heart rate to 66 per minute and of the circulation time to 25 seconds, and the increase in the femoral arteriovenous oxygen difference to 4.09 volumes per cent. The venous pressure had risen slightly to 13.5 cm H₂O. There was also a striking change in the clinical appearance of the patient. His face, previously bright pink, was now definitely cyanotic, the hands and feet were quite cool, only the faintest sound could be heard over the carotid artery and no sound over the femoral or brachial arteries.

Four days after vitamin therapy was instituted the heart rate was 52 per minute, the blood pressure had risen to 152 mm Hg systolic and 90 diastolic, the vital capacity had increased to 3,100 cc and the patient had lost 12 pounds of edema fluid, in spite of the fact that there was no essential change in the venous pressure or colloid osmotic pressure of the blood. Marked clinical improvement coincided with these circulatory changes. In 10 days following the vitamin therapy the patient had lost 20 pounds of weight, and the vital capacity, the blood pressure, heart rate, venous pressure and femoral arteriovenous oxygen difference had returned to normal. An interesting change in the electrocardiogram at this time was the inversion of the T-wave in Lead I, which subsequently reverted to normal (figure 11).

At the beginning of the third week the parenteral injection of vitamin B₁ was stopped, and a high vitamin diet started. The knee jerks returned in the middle of the fourth week. At the end of the fourth week a second course of parenteral vitamin B₁ was given, exactly as before, with no effect on any aspect of the circulation.

The patient was discharged well at the end of the sixth week.

Case 4 Congestive failure of the circulation, the only manifestation of vitamin deficiency, when treated with digitalis and diuretics showed little improvement, on vitamin B₁ striking improvement. J. F., an unemployed waiter, aged 60 years, for four years had spent but 25 cents a day on food which was grossly inadequate in vitamins. He had taken an average of 10 glasses of ale and 2 glasses of whisky daily for one year. He complained of cough for six months, dyspnea on exertion for one month, orthopnea for two weeks, increasing dependent edema for 10 days and swelling of the abdomen for one week.

The family history showed that one brother died of alcoholism. The past history was non-contributory.

Physical examination showed an elderly, apparently well-nourished man, with severe orthopnea, and extreme dyspnea on the slightest exertion. His color was cyanotic, but at times only slightly so. There was marked dependent edema up to the sternum. The skin of the face and extremities was warm and dry. There was moderate engorgement of the veins of the neck. The heart was percussed 11 cm to the left and 5 cm to the right of the midsternal line. There was a rough blowing systolic murmur heard over the entire precordium, loudest at the apex. The heart rate was 120 per minute and the rhythm was regular except for occasional extrasystoles. The arterial pressure was 140 mm Hg systolic and 80 diastolic. Loud sounds were heard over the carotid and femoral arteries. Percussion of the chest revealed diminished resonance posteriorly at both lung bases, where moist rales were heard. The abdomen was tensely distended, with shifting dullness in the flanks and a palpable fluid wave. No organs were felt. The neurological examination was negative. Temperature 98° F. Respirations 30 per minute. Weight 184 pounds.

Laboratory studies. *Urine*, acid, specific gravity 1.015, albumin 0, sugar 0, bile 0, acetone 2 plus, diacetic acid 0, pyruvic acid 0, sediment, many leukocytes. *Blood*, hemoglobin 85 per cent, erythrocytes 3,700,000 per cu mm, leukocytes 12,400, neutrophils 85 per cent. The non-protein nitrogen was 28 mg per 100 cc, the fasting

blood sugar 94.1 mg per 100 cc and the carbon dioxide capacity 79.2 volumes per cent. The total protein content of the plasma was 4.8 gm per 100 cc, albumin 2.57 gm, globulin 2.23 gm, calculated osmotic pressure 178 mm H₂O. Icterus index 20. The Hinton test was negative. The Takata-Ara test was positive. Bisulphite binding substances in the blood (calculated as pyruvic acid) were 12.89 mg per 100 cc. *Lidema fluid* from the thighs showed a total protein content of 0.34 gm per 100 cc,

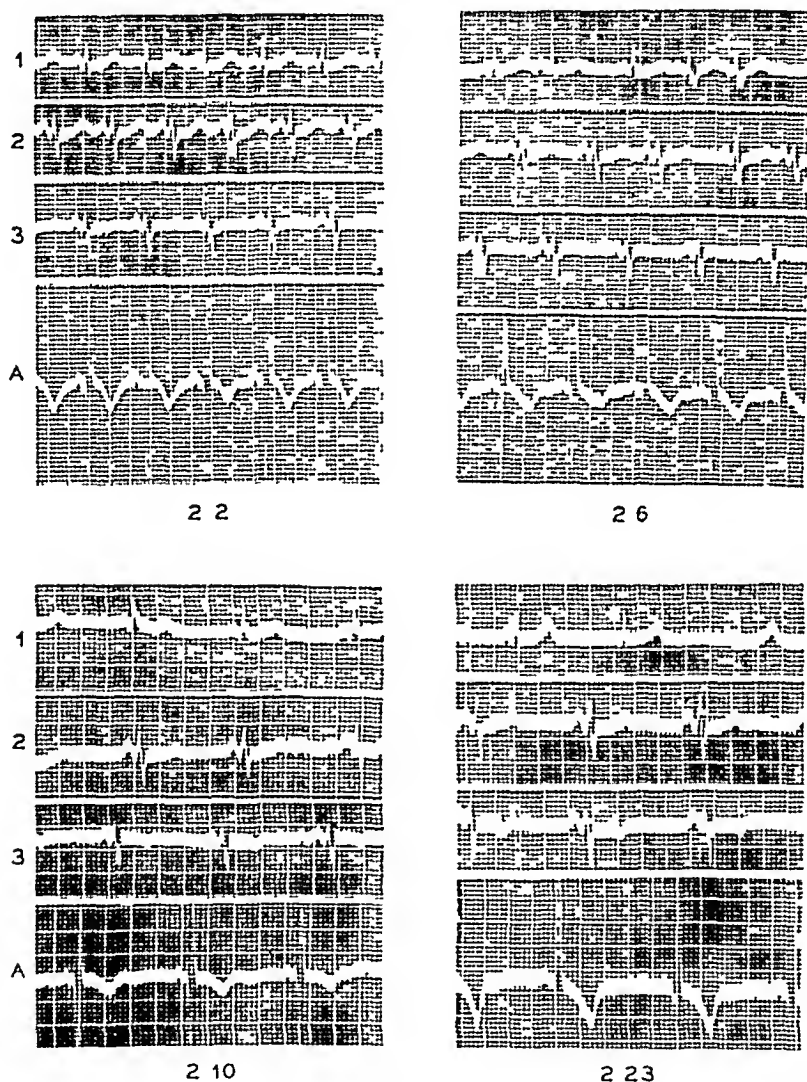


FIG 12 Electrocardiograms in Case 4. Note changes in rate and in T-waves.

albumin 0.095 gm, globulin 0.234 gm. The vital capacity was 1000 cc and the venous pressure 17 cm H₂O. The electrocardiogram showed tachycardia, low voltage (6 mv) and prolonged Q-T interval (K equals 0.52), suggesting myocardial disease (figure 12).

Because of the patient's precarious condition, his age, and the finding of a loud systolic murmur at the apex of the heart, it was deemed wise to treat him at once with

the standard cardiac drugs but to withhold vitamin therapy. Accordingly, he was put on a Karel diet (boiled milk), was digitalized rapidly and was given ammonium chloride, Aminophyllin and Salyrgan (two doses of 2 c c intravenously) as diuretics. Morphia was used as a sedative with marked subjective relief. There was a fall in pulse rate but no diuresis—the daily output ranged from 700 to 1,100 c c. This regime was maintained for four days, and on the fifth day the following observations were made: arterial pressure 145 mm Hg systolic and 82 diastolic, heart rate 80 per minute, venous pressure 15 cm H_2O , circulation time 13 seconds, femoral arteriovenous oxygen difference 3.66 volumes per cent. The vital capacity was 1,250 c c. The

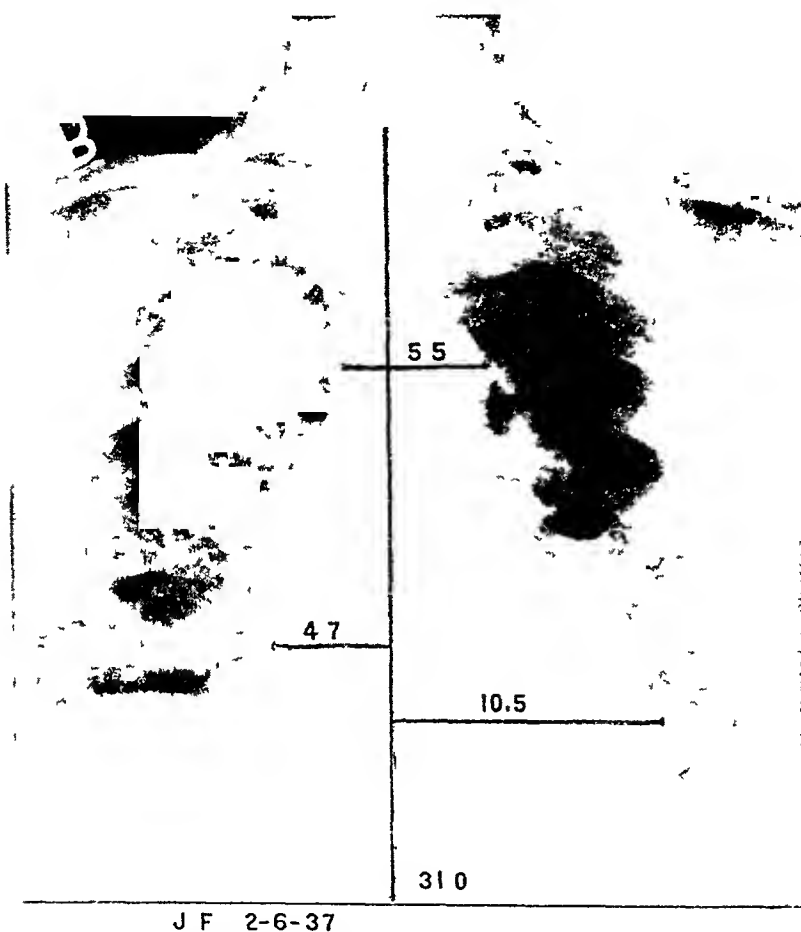


FIG 13 The cardiac shadow in Case 4 before vitamin B_1 treatment.

total protein content of the blood plasma had risen to 5.38 gm per 100 c c, albumin 2.67 gm, globulin 2.71 gm, producing a calculated osmotic pressure of 200 mm H_2O . This was evidence of hemoconcentration, as the values two days later had fallen to and below their previous levels. A 7-foot roentgenogram showed the heart still enlarged to the left and right (figure 13).

On the fifth day *all medication* was omitted, and the deficient diet continued unchanged. Synthetic crystalline vitamin B_1 was given in 10 mg doses subcutaneously five times a day. The next day the urine output was 1,500 c c and rose progressively to reach a peak of 4,800 c c four days after the vitamin was started.

The clinical course and circulatory measurements are shown in chart 3. Of particular interest on the second day after vitamin therapy were the elevation of the blood pressure to 160 mm Hg systolic and 90 diastolic, the slowing of the heart rate to 60 per minute, the increase in the circulation time to 25 seconds and the increase in the arteriovenous oxygen difference to 48 volumes per cent. The venous pres-

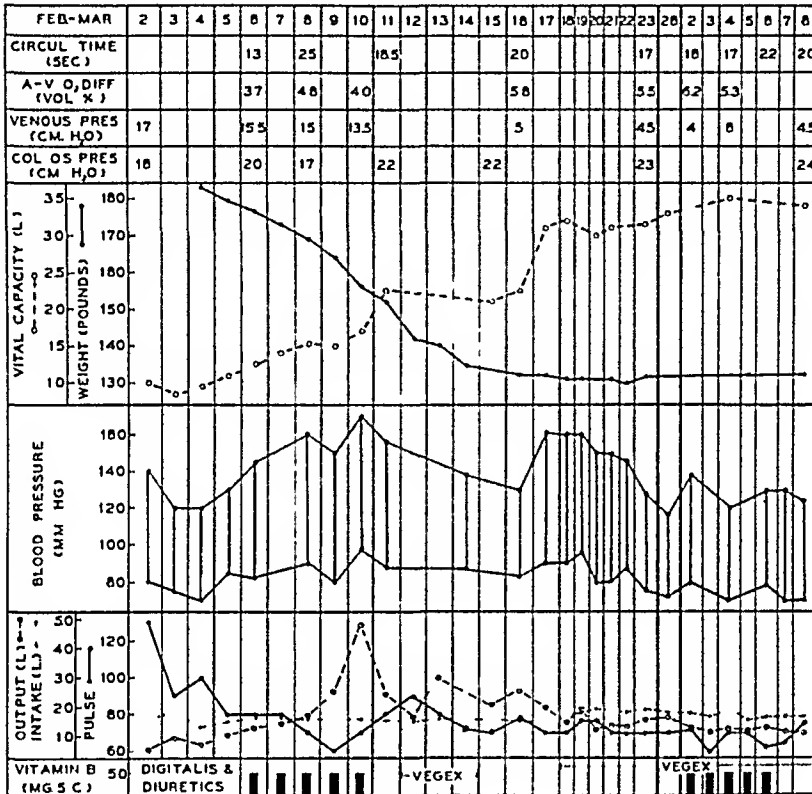


CHART 3 The clinical course in Case 4

sure and colloid osmotic pressure of the blood were still essentially unchanged, but subsequently became normal, as did the blood pressure, the heart rate and other aspects of the circulation.

The clinical improvement coincident with these changes was dramatic. Except for a brief febrile episode with signs of bronchopneumonia on the sixth day after vitamin treatment, the course was one of steady improvement. The patient lost 51 pounds of weight in 12 days. He was then seen to be a thin-faced, frail individual, rather than the well-nourished man he had seemed on admission. The cyanosis, the orthopnea and the dyspnea on exertion disappeared, while the vital capacity rose to a normal value.

On the eleventh day a high vitamin diet was begun. In the fifth week, when all the circulatory measurements had been normal for one week, the same course of vitamin B₁ was repeated with no effect whatever. The patient was discharged well at the end of the fifth week. The 7-foot roentgenogram (figure 14) showed that the heart had returned to normal size.

Case 5 Congestive failure of the circulation, cardiac asthma, polyneuritis, mild psychosis, improvement on high vitamin diet and continuous high alcohol intake

O O, a corsetiere, aged 37 years, had consumed one pint of whisky daily for seven years. Her diet was meager, rarely contained vegetables or meat, and consisted principally of coffee, tea, and sandwiches of white bread.

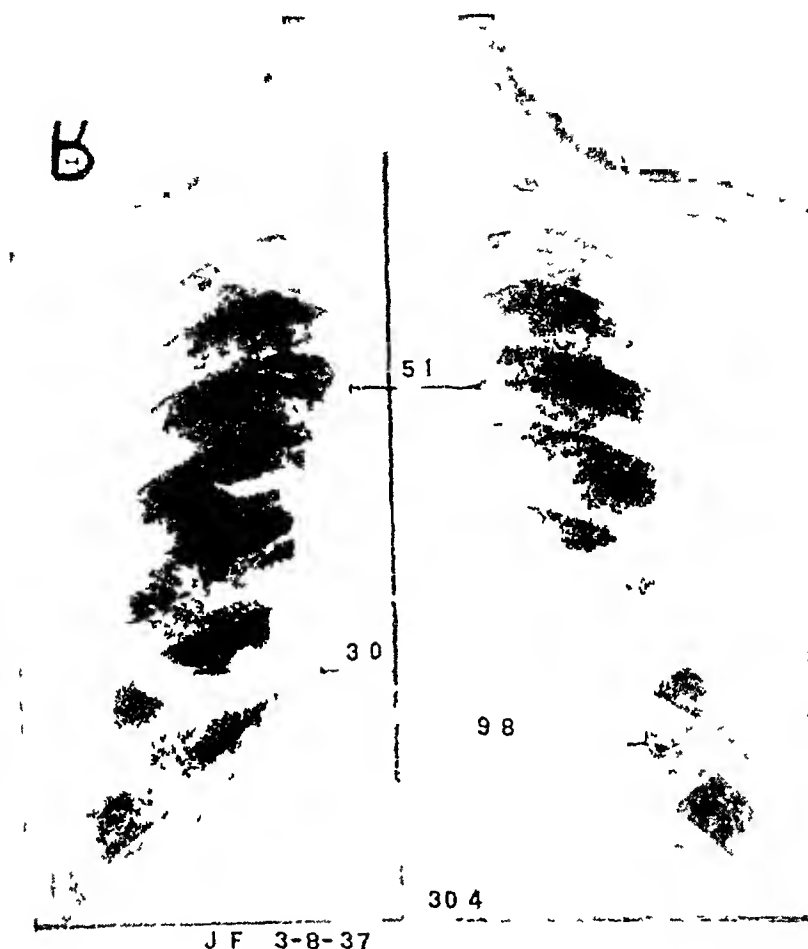


FIG 14 The cardiac shadow in Case 4 after improvement

She complained of intermittent weakness and numbness in the feet for six years, increasing and progressing upward to involve the legs and finally the hands for three months. For two years she had had palpitation and dyspnea on exertion, and for one year swelling of the ankles. She also complained of orthopnea for three weeks, and nocturnal attacks of paroxysmal dyspnea for two weeks.

The family history revealed that the paternal relatives were alcoholics, otherwise it was non-contributory. The past history was non-contributory.

Physical examination showed a well-nourished, mildly psychotic, apprehensive orthopneic woman with marked edema of the legs. The skin was thick, warm and moist. The veins of the neck were distended. The heart was percussed 11 cm to the left and 5 cm to the right of the midsternal line. There was a gallop and a short blowing systolic murmur at the apex. The heart rate was 120 per minute and the rhythm was regular. The arterial pressure was 110 mm Hg systolic and 70 diastolic. The carotid and peripheral arteries showed increased pulsations. The lungs were resonant and clear. In the abdomen the liver edge was felt just below the right

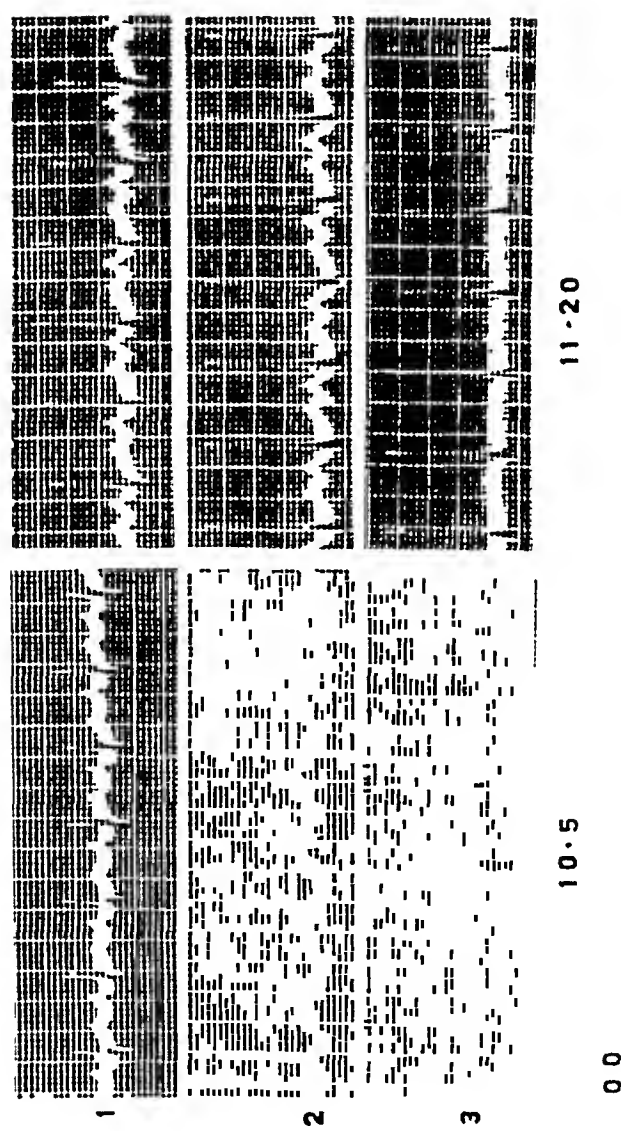


FIG 15 Electrocardiogram in Case 5. Note the return of the S-T complexes to normal following the continued administration of oral vitamin B concentrate and alcohol

costal margin There was bilateral toe drop, absent knee and ankle jerks, and absent vibration sense below the knees Temperature 99° F Respirations 25 per minute Weight 167 pounds

Laboratory studies *Urine*, acid, specific gravity 1.019, albumin 0, sugar 0, sediment, many leukocytes *Blood*, hemoglobin 82 per cent, erythrocytes 4,230,000 per cu mm, leukocytes 9,300, neutrophils 76 per cent The non-protein nitrogen was 60 mg per 100 cc of blood The total protein content of the plasma was 6.5 gm per 100 cc, albumin 3.25 gm, globulin 3.25 gm, with calculated osmotic pressure 264 mm H₂O The Kahn test was negative Roentgenogram confirmed the enlargement of the heart and showed congestion of the lung fields Electrocardiogram (figure 15) showed tachycardia, and abnormal T-waves suggesting myocardial disease

For five days the patient was kept on a house diet with no essential change in her condition She was then placed on a high vitamin diet, supplemented by oral yeast extracts and intramuscular liver extract In addition she was given one pint of whisky a day On this regime she improved rapidly The nocturnal dyspnea, the edema and palpitation disappeared Within two weeks the heart rate had decreased to 90 and the gallop had disappeared After six weeks the electrocardiogram was normal (figure 15) There was slower but steady improvement in the neurological and mental symptoms When discharged from the hospital, four months after entrance, she was able to walk satisfactorily and the psychosis had cleared, but some abnormal neurological signs still persisted in the legs She had continued to receive one pint of whisky daily until discharge

Case 6 *Acute cardiac dilatation and congestive failure associated with polyneuritis, improvement after rest, digitalis, good diet and oral vitamin "B" extract* W F, a laborer, aged 32 years, had consumed ½ pint of pure alcohol daily for five years He had eaten little food because of an extremely poor appetite He complained of increasing dyspnea on exertion for two years, increasing swelling of the legs for one year, and difficulty in walking associated with numbness of the feet and hands for six months The family history and the past history were non-contributory

Physical examination revealed a small but well-nourished man, comfortable, flat in bed with marked edema of the lower legs The skin was dry, warm and of good color The veins of the neck were distended and showed marked pulsations The heart was percussed 11 cm to the left and 6 cm to the right of the midsternal line The precordium was heaving rapidly A marked gallop was heard near the apex, where there were also loud, rough systolic and diastolic murmurs Over the aortic area blowing systolic and diastolic murmurs were heard The heart rate was 100 per minute and the rhythm was regular The arterial pressure was 130 mm Hg systolic and 60 diastolic There were marked pulsations of all peripheral arteries, over which loud "pistol" sounds were audible The lung bases were dull posteriorly In the abdomen the liver was palpated 4 cm below the right costal margin The knee and ankle jerks were not obtainable Temperature 100° F Respirations 20 per minute Weight 113 pounds

Laboratory studies *Urine*, first specimen acid, specific gravity 1.036, albumin 0, sugar 3 plus, bile positive, acetone 0, diacetic acid 0, sediment, negative Later specimens negative *Blood*, hemoglobin 78 per cent, erythrocytes 4,220,000 per cu mm, leukocytes 9,800, neutrophils 65 per cent The non-protein nitrogen was 22 mg per 100 cc, the fasting blood sugar on the third day 93 mg per 100 cc The total protein content of the blood plasma was 6.3 gm per 100 cc, albumin 3.4 gm, globulin 2.9 gm, with calculated osmotic pressure 260 mm H₂O The Kahn test was negative The Takata-Ara test was negative

A 7-foot roentgenogram of the heart on the second day showed enlargement (Figure 16) The electrocardiogram showed a flat T-wave in Lead I and prolonged Q-T interval (K equals 0.46), interpreted as myocardial disease

Because of the diastolic murmurs heard on admission it was thought that the patient had organic valvular heart disease. He was digitalized rapidly and given a high vitamin diet supplemented by oral extracts of vitamin B. On the second day no diastolic murmur could be heard. The improvement was rapid. On the seventh day he was allowed out of bed. The digitalis was omitted. A 7-foot roentgenogram at the beginning of the fifth week (figure 17) showed a small heart. He was discharged well in the sixth week.

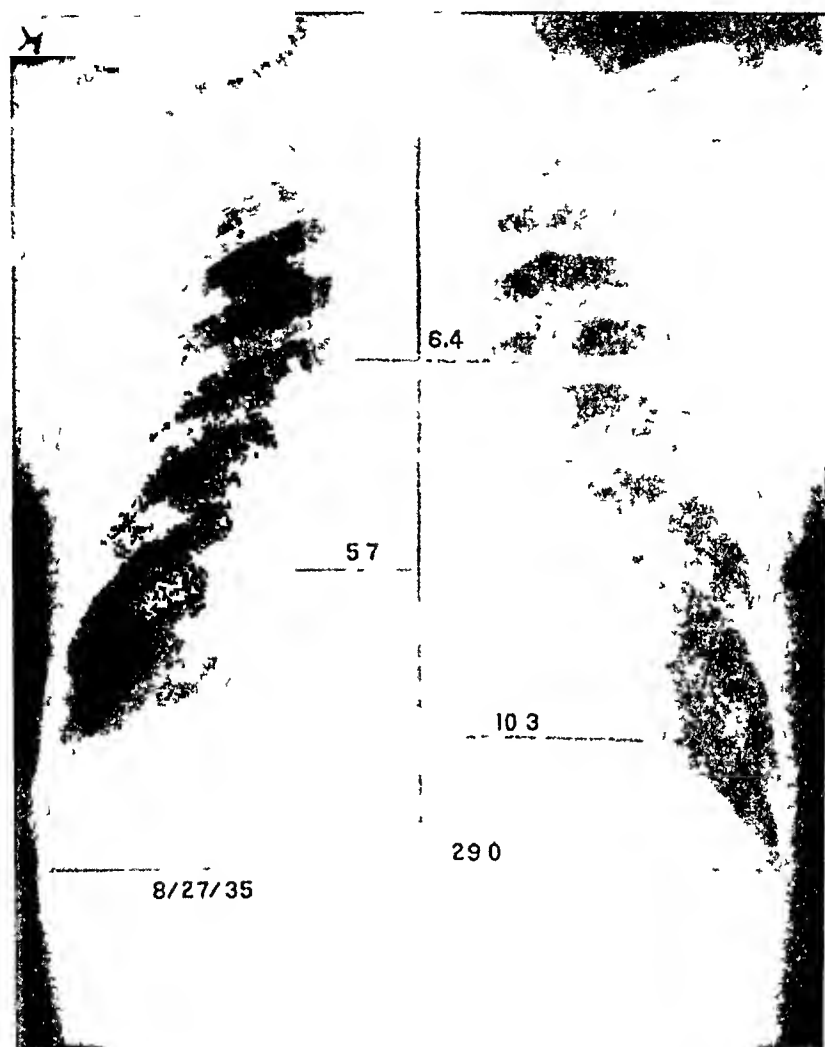


FIG 16 The cardiac shadow in Case 6 on the first day after admission

Case 7 Repeated admissions for attacks of carotid sinus syncope and circulatory failure associated with polycystitis, relief after diet and extracts rich in vitamin "B" E. S., an unemployed odd-job man, aged 47 years, had drunk one pint to one quart of liquor daily for years. He had eaten irregularly and his diet was of poor quality. He was admitted to the hospital on three occasions with essentially the same complaints. These were dizziness and attacks of syncope, soreness of the mouth and tongue, pain, weakness and numbness in the legs, nocturnal cough, dyspnea on exertion and nocturnal attacks of paroxysmal dyspnea.

Physical examination revealed a poorly nourished man with no orthopnea or edema. The skin was pale. The mucosa of the mouth and tongue was red, with patchy ulcerated areas covered by whitish exudate. The heart was percussed 7 cm to the left and 3 cm to the right of the midsternal line. There was a blowing systolic murmur at the apex. The heart rate was 110 to 120 per minute, and the rhythm was regular. The arterial pressure was 115/70 to 120/90 mm Hg. The abdomen was

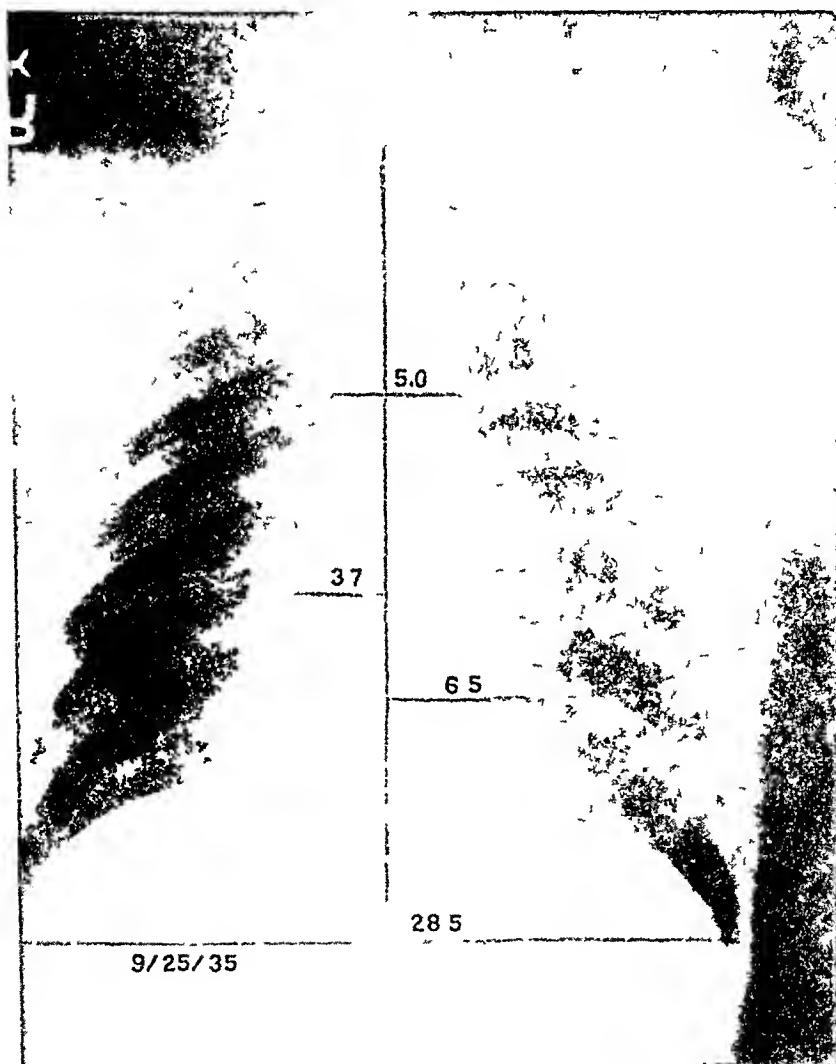


FIG 17 The cardiac shadow in Case 6 following improvement

negative. The ankle jerks were not obtainable and the vibration sense was absent below the knees. Temperature 99° to 100° F. Respirations 20 to 25 per minute. Weight 135 to 145 pounds.

Laboratory studies. *Urine*, acid, specific gravity 1.020, albumin, bile, sugar and sediment negative. *Blood*, hemoglobin 55 per cent, erythrocytes 4,000,000 per cu mm, leukocytes 5,700, neutrophils 71 per cent. The non-protein nitrogen was 30 mg per 100 cc. The Kahn test was negative. *Lumbar puncture* revealed normal pressure and normal spinal fluid. *Gastric analysis* showed no free acid after his-

tamine. The 7-foot roentgenogram showed no abnormality of heart or lungs. The electrocardiogram showed flattening or inversion of the T-waves in Leads I and II, interpreted as myocardial disease.

On each admission under treatment with a good rest, intramuscular liver and vitamin "B" extracts, there was complete relief of the cardiovascular symptoms within two weeks. It is of interest that with improvement the blood pressure rose from 140/104 to 200/120 mm Hg. The improvement in the neurological symptoms was equally striking, but slower.

On the second admission it was found that even mild stimulation of the carotid sinus caused complete asystole of the heart and syncope. The patient stated that the induced attack was the same as the spontaneous spells of which he complained. Six days after vitamin therapy the dizziness had improved, and carotid sinus pressure now induced no asystole but an idioventricular rhythm with a rate of 30 per minute. Slight dizziness but no syncope accompanied the slowing. Four days later, and thereafter, stimulation of the carotid sinus induced only transient physiological slowing of the sinus rhythm and no dizziness. He was discharged improved in the third week.

DISCUSSION

The association of cardiovascular dysfunction with nutritional deficiency suggests a possible causative interrelation between the two conditions. Furthermore, the characteristics of the cardiovascular disturbances and the frequent coexistence of nervous disorders indicate a similarity between the condition observed and oriental beriberi. It was the primary purpose of this investigation to ascertain whether the disease studied is only similar to or is actually identical with the cardiovascular disturbances occurring in beriberi.

Beriberi is considered to be primarily an avitaminosis, and the polyneuritic form of the disease has been reproduced experimentally in animals fed a diet lacking in vitamin B₁. In spite of the fact that a descriptive knowledge of this disease dates back to ancient Chinese and Japanese records, the etiology and pathogenesis are but partially clarified. The cardiac form of the disease has heretofore been studied only in the Orient. In recent years particularly, extensive investigations on "beriberi heart" have been carried out in Java by Wenckebach and Aalsmeer^{10, 11}.

The Occurrence of Beriberi in the United States As recently as 1932 Wenckebach¹³ stated that "beriberi is, or is supposed to be an avitaminosis, which is met in such tropical countries only where rice is the prevailing food." Nevertheless, scattered reports are available on the occurrence of beriberi in other parts of the world, including the United States. Scott and Herrmann¹⁴ have reported cardiac manifestations among rice workers in Louisiana. Kep'ler¹⁵ has observed one and Riesman and Davidson¹⁶ two suggestive cases with cardiac manifestations. There are also a few reports on polyneuritis due to food deficiencies, in which the authors considered the clinical syndrome identical with beriberi. Wohl¹⁷ described such a poly-

* Since this paper was sent in for publication, B. Sure and W. A. Jones have reported (personal communication) a study on the role of vitamin B₁ in cardiovascular diseases in 30 patients at the U. S. Veteran's Hospital, Fayetteville, Arkansas.

neuritic form of beriberi in a young diabetic patient who lived on an unbalanced diet

Minot, Strauss and Cobb concluded that in alcoholic polyneuritis the etiological factor is vitamin B deficiency, rather than excessive use of alcohol. Jolliffe, Colbert and Joffe¹⁸ have demonstrated that, according to Cowgill's formula, the vitamin B (B_1) intake of alcoholic patients with polyneuritis is decreased to well within the limit required for the induction of polyneuritis in animals. Among the patients with polyneuritis and pellagra whose records are on file in the Boston City Hospital, consumption of a large amount of alcohol, usually over a prolonged period, frequently occurred. In comparing the clinical characteristics of "alcoholic pellagra" and "nonalcoholic pellagra," Spies¹⁹ observed no difference between the two types. Our clinical experience, similarly, fails to reveal any difference between alcoholic and nonalcoholic deficiency polyneuritis and pellagra. These considerations strongly suggest that the polyneuritis and pellagra observed in both alcoholic and nonalcoholic patients with food deficiency are of similar, if not identical, etiology, and that both of these conditions bear a causative relationship to the avitaminosis.

"Beriberi Heart" as Heretofore Described There are mainly two explanations of the pathogenesis of "beriberi heart." The older theory, advocated by early Japanese workers, is that the cardiac disease is caused by a disturbance of the function and a "degeneration" of the *vagus nerves*.²⁰ The frequent observation of rapid heart and the demonstration of demyelination of the vagus nerves were offered as evidence for this theory. The histological evidence of structural changes in peripheral nerves is, however, inadequate. Some of the cases studied by us showed histological changes within the vagus centers.

Lately the vagus theory has given way to the myogenic theory. Wenckebach¹³ considers the essential change in the heart to be degeneration of the muscle which "robs the heart of its means of resistance to stretching, and deadens its power of contractility." In addition there is widening of the peripheral arterioles which results in a rapid and increased volume flow to the right side of the heart. The right ventricle, unable to take care of this inflow, becomes dilated and the syndrome of right ventricular failure develops. According to these investigators, dilatation of the right side of the heart, in the presence of clear lungs as evidenced by physical and roentgen-ray examinations, and the exaggeration of peripheral vascular signs after the administration of epinephrine and their diminution after pitressin constitute the main characteristics of "beriberi heart." The reports of Keefer²¹ and others indicate, however, that the most common disturbances in "beriberi heart" in China are tachycardia, palpitation and excessive fatigue, and that pure right-sided dilatation is not an essential manifestation.

Aalsmeer and Wenckebach^{10,11} observed no essential electrocardiographic changes in patients with "beriberi heart" in Java. At times pa-

tients with severe circulatory disturbances showed a *shortened* P-Q conduction time, which became normal as the condition improved. Keefer²¹ has described low voltage and negative T_r waves in some of the cases observed in China.

Cardiovascular Changes in Experimental Vitamin B₁ Deficiency So far as is known at present, deficiency of vitamin B₁ is the only vitamin deficiency which is followed by cardiac disturbances.* Carter and Drury²² showed that pigeons fed a diet of polished rice developed bradycardia and heart-block. These changes were of vagal origin, as section of the nerve or atropine abolished them. In an electrocardiographic study of vitamin B deficiency in the rat, Drury, Harris and Maudsley²³ observed a bradycardia of 300 or 350 per minute, as compared with a normal rate of 500 to 525. In this animal the bradycardia was of sinus origin, and not due to vagal influence. So characteristic is this response that it is used to test diets for vitamin B₁ deficiency. These observations show that the cardiac disturbance can vary in different species.

The experimental studies did not reveal changes in the complexes of the electrocardiograms. As far as one can ascertain, however, the electrocardiograms obtained in rats were not standardized. Because the patients with nutritional deficiencies showed changes in the electrocardiographic complexes, a study was undertaken to ascertain whether similar changes develop in the standardized electrocardiograms of rats deficient in vitamin B₁.²⁴ The results of this study indicate that rats on B₁ deficient diets develop not only bradycardia but also changes in the electrocardiographic complexes, such as increased height of the S-T segment and flattening or inversion of T-waves. Subcutaneous administration of from 5 to 28γ of crystalline vitamin B₁ (Merek) abolished within 6 to 12 hours both the bradycardia and the changes in the complexes. These electrocardiographic changes are in harmony with those described in human beings.

Central Nervous System Changes in Experimental Vitamin B₁ Deficiency That deficiency of vitamin B₁ is associated with failure in certain oxydase systems has been known since 1918.²⁵ Peters and his associates^{27, 28} have shown that in vitamin B₁ deficiency the oxygen utilization of the brain is reduced. After adding vitamin B₁ to deficient brain tissue of the pigeon and the rat *in vitro*, the oxygen consumption increased and the pyruvate formed by the avitaminous brain decreased. The degree of biochemical change was not the same in all parts of the brain. These workers concluded that the symptoms of avitaminosis observed in the rat and pigeon are of central origin.^{28, 29} Church³⁰ has shown that the vestibular function is significantly altered in rats with vitamin B (B₁) deficiency. The fact that these striking changes in function, referable to vestibular nuclei, disappeared within as short a period as a few hours indicates that a central metabolic disturbance, rather than organic degenerative lesions, was responsible.

* It is probable that the myocardial disturbances reported in rickets and scurvy are caused by the simultaneous presence of vitamin B₁ deficiency.

Evidence of the Nutritional Origin of the Cardiovascular Dysfunctions

The following evidence supports the nutritional and particularly the vitamin B₁ origin of the disturbances of the cardiovascular system described (a) In the majority of the cases studied there was unbalanced food intake with adequate supply of calories and with maintenance of normal body weight. A calculation of the vitamin B₁ content of the food in relation to the caloric intake was below the normal requirement of man and within the limit necessary for the development of B₁ deficiency, as indicated by Cowgill. The diet of these patients was therefore similar to that described recently by Jolliffe, Colbert and Joffe¹⁸ in alcoholic addicts with polyneuritis. In a smaller group of patients the vitamin "B" intake seemed to be adequate but the presence of changes in the gastrointestinal canal apparently prevented its utilization. (b) None of the recognized etiological factors of cardiovascular disease were present in the "pure" cases studied. The clinical, physiological and morphological findings did not correspond to those observed in the recognized diseases of the cardiovascular system. (c) The cardiovascular disturbances were frequently associated with disturbances in other systems, which were of the type attributed to vitamin "B" deficiencies. (d) Just as in oriental beriberi, the patients with a severe degree of circulatory failure were not apt to have severe polyneuritis, and vice versa. (e) The dilatation of the peripheral arterioles, the relatively or absolutely increased velocity of blood flow with increased venous pressure, the dilated heart, the severe generalized edema, the vascular sounds associated with bounding pulsation, as well as the occurrence of vasomotor collapse, indicate a similarity between "beriberi heart" as described in the Orient and the condition observed in Boston. (f) The electrocardiographic changes observed in human beings are similar to those found in rats deficient in vitamin B₁. (g) All the characteristics of the disturbances observed in man usually disappear after rest and the administration of vitamin B₁ or a diet rich in vitamin B₁.

Differences Between the Circulatory Disturbances Observed and Those Reported in "Beriberi Heart" There were a number of differences between the characteristics of the cardiovascular dysfunctions observed in Boston and those described as "beriberi heart" in the Orient. In contrast to the patients observed by Aalsmeer and Wenckebach in Java, the group here reported usually did not exhibit a pure right-sided failure of the circulation. Patients with cardiac dilatation, peripheral arterial sounds, rapid peripheral flow and engorged veins were observed, but other patients with an identical type of deficiency showed pulmonary engorgement with dyspnea, cardiac asthma, orthopnea and other manifestations of left-sided failure. In a few patients vasomotor collapse developed in its pure form. Electrocardiographic changes with tachycardia were present in some patients without any other abnormality. There were again instances in which at different stages of the disease various combinations of these changes occurred.

Hence the cardiovascular disturbances caused by nutritional defects do not form a rigid clinical syndrome. We wish also to emphasize that the term "beriberi heart" is inappropriate because of the widespread nature of the circulatory disturbances in this disease. Wenckebach himself indicates that the primary change is a peripheral dilatation, and that the heart is only secondarily involved. Whether the clinical differences between oriental "beriberi heart," particularly as described in Java, and the cardiovascular disturbances in the group here reported are due to actual differences in some aspects of their pathogenesis, or to the fact that the type reported by Aalsmeer and Wenckebach represents but one form of the disease existing in Java, it is impossible to state. In the production of vitamin deficiencies in animals, factors other than vitamins play important rôles. In man, in the majority of instances there are multiple avitaminoses, and the number of variables is even greater. The composition of the food, the functions of internal secretory glands, the intensity of muscular work, and the time element in the development of the deficiency may well have an important bearing on the variability of the clinical picture. The relative significance of the interrelation between these factors is not known at present.

In the Orient it is recognized that persons who perform strenuous muscular exercise, and who do not exhibit polyneuritis, form the group which is liable to develop cardiac dilatation and other circulatory symptoms. In this part of the United States vitamin "B" deficiencies occur mainly in alcoholics, and less frequently in pregnant women, in persons without work and hence in poverty, in "food cranks," in patients with diabetes or with certain types of gastrointestinal diseases. Such persons seldom, if ever, perform prolonged hard work. This may well be important in determining the somewhat different aspect of the disease as observed in the Orient and in Boston. That deficiency of vitamins is not the sole determining factor in these clinical syndromes is clearly indicated by the fact that not all patients with the same degree of vitamin deficiency develop symptoms, and also by the fact that the same degree of deficiency can produce different symptoms in different subjects. Furthermore pure vitamin deficiency, particularly a deficiency of B₁ (polyneuritis) or of B₂ (pellagra), is rare. In the majority of cases on record in the Boston City Hospital pellagra and polyneuritis occurred in combination. On the other hand, polyneuritis and pellagra were rarely associated with an *advanced* degree of scurvy.

Changes in the Electrocardiogram and Their Relation to Vitamin B₁
The electrocardiographic changes observed by us were essentially the same as those reported recently by Feil³¹ in a group of patients with pellagra. It is significant, however, that in our group with nutritional deficiencies, electrocardiographic changes of identical nature were observed not only in pellagra without polyneuritis, but also in polyneuritis without pellagra, and in cases with food deficiency without either pellagra or polyneuritis. Conversely, electrocardiographic changes were not necessarily present in all pa-

tients with any of these deficiencies. In view of the fact that similar electrocardiographic changes were induced in rats with vitamin B₁ deficiency, and in patients without pellagra, we attribute the electrocardiographic changes to deficiency of vitamin B₁ rather than of other fractions of the "B" group. It is of interest and in harmony with observations in man that in the same rat the electrocardiographic changes may be different or may even be absent in repeated instances of vitamin B₁ deficiency. This is further evidence that in B₁ avitaminosis the disturbances even within one organ, such as the brain or heart, may vary, depending upon their particular focal localization.

Porter and Higginbotham³² have claimed recently that not a single case of pellagra observed by them exhibited congestive failure of the circulation or increase in the size of the heart. They conclude that in pellagra no characteristic change occurs in the cardiovascular system and that pellagra and beriberi have no comparable effect on the heart. This difference, according to Porter's belief, is absolute and means that vitamin B₁ is not concerned with the pathogenesis of pellagra. He ventures that "many of the diseases produced by avitaminosis affect, in a selective manner, certain tissues of the body, and one can anticipate precisely the kind of deficiency by noting the structures involved and the character of the tissue reactions." Porter interprets the electrocardiographic changes observed in pellagra as having no relation to beriberi or to deficiency of vitamin B₁. In support of this he quotes Wenckebach's "unequivocal statement" that the electrocardiogram in beriberi is normal, with the exception that the conduction time is shortened. Such a contention is not in agreement with our findings. Our interpretation of our own observations, as well as of those of Feil and of Porter, is that the cardiovascular disturbances in vitamin "B" deficiencies are more varied than is claimed by Wenckebach in beriberi or by Porter in pellagra, and that deficiency of B₁ is the primary cause for all these disturbances. Cardiovascular disturbances are apt to be present in pellagra as well as in beriberi, because in man vitamin B₁ deficiency usually occurs in combination with B₂ deficiency.

The Rôle of Alcohol As the majority of the patients observed consumed large amounts of alcohol, the rôle of alcohol in the development of cardiovascular manifestations requires special consideration. There is valid evidence indicating that alcohol per se cannot be primarily responsible for the manifestations observed. In the first place, chronic alcoholism is exceedingly common, while the condition described is relatively rare, hence a simple causative relationship does not exist. Furthermore, pharmacological studies do not reveal that pure alcohol per se causes persistent cardiovascular damage or polyneuritis, such as occurs in beriberi. In a group of patients with polyneuritis associated with alcoholism Strauss³³ has shown that the polyneuritis improved following the administration of vitamin B extracts and of amounts of alcohol similar to those consumed by

the patient during the development of the polyneuritis. Four patients of the group studied by Strauss, who are included in our series, showed cardiovascular changes which improved under the experimental therapeutic regime *containing alcohol*. Further evidence against the primary rôle of alcohol is that in spite of the fact that many of the patients with severe degrees of circulatory failure and polyneuritis discontinued the consumption of alcohol many weeks before the observations were made, the condition grew rapidly worse or actually developed during the withdrawal period. This was particularly true in patients with persistent anorexia, nausea, vomiting and diarrhea. If alcohol, a rapidly oxidizable substance, were a primary "toxic agent" this would not be likely to occur.

In the light of present knowledge, nevertheless, we attribute to alcohol the following *secondary* predisposing roles in the precipitation of the cardiovascular dysfunctions and of vitamin deficiencies in general. (a) Alcohol is a food substance *par excellence* in this part of the world, and it supplies the body with the necessary calories but with a minimum of vitamin "B," an ideal combination of factors for the development of "beriberi." It should be recalled that the caloric value of a pint of pure alcohol is about 3,500 calories. In addition, the consumption of large amounts of alcohol tends to produce gastritis, achlorhydria, persistent nausea and diarrhea, which in turn further interfere with the utilization of vitamin "B." Such patients frequently claim that even with special effort they are unable to take appreciable amounts of food (Case 6). (b) There is possibly another specific, though secondary, role of alcohol in beriberi. It is known that the composition of the diet in terms of carbohydrate, protein and fat has a significant relation to the development of beriberi. Abderhalden and Wertheimer³⁴ have demonstrated that if vitamin B deficient pigeons are fed fatty acids instead of carbohydrates, muscular cramps characteristic of the deficiency do not develop. Several observers have claimed that a high carbohydrate diet in animals and a pure rice diet in man predispose to clinical vitamin B₁ deficiencies. Alcohol, as a carbohydrate, in large amounts may act in the same way. The tendency of diabetic patients to develop polyneuritis and cardiovascular dysfunction is probably due to the combined effects of an abnormal metabolism and a high carbohydrate, low vitamin diet.

The importance of alcohol in vitamin B deficiency has been demonstrated experimentally by the recent study of Wechsler, Jervis and Potts³⁵. These investigators showed that the severity of the nervous symptoms of monkeys maintained on alcohol and a vitamin B₁ deficient diet cannot be referred to the avitaminosis alone. The clinical course of the B₁ avitaminosis was aggravated by continuous alcohol intoxication. They concluded that the combination of alcohol and B₁ avitaminosis is particularly noxious to the nervous system.

Pathogenesis of the Cardiovascular Dysfunctions The results of

animal experimentation favor the concept that most of the manifestations of B_1 deficiency depend on disturbances of nervous functions, particularly in the central nervous system^{29, 30} The most frequent manifestations of beriberi in the Orient, as well as in the United States, consist in polyneuritis, psychosis, vertigo, cough and dysphagia, which are also nervous in origin The question then arises as to whether the cardiovascular dysfunctions depend primarily on nervous, on local myocardial or on vascular changes The instances of tachycardia followed by bradycardia, as well as the instances of irritable carotid sinus reflex, indicate that some of the manifestations depend on disturbance of the vagus system The tendency to vasomotor collapse and the dilatation of peripheral arterioles, which constrict after the administration of crystalline B_1 , may be, at least theoretically, central in origin Some of the changes, especially those in the electrocardiogram, may be due to local myocardial disturbances Other manifestations, such as cardiac dilatation, are explicable as secondary to the rapid peripheral blood flow The exact pathogenesis of the cardiovascular dysfunctions, however, is not known at present

The response of patients with beriberi to therapeutic measures also requires further study Patients observed by us as well as those observed in China and in Labrador show considerable variation in rate of improvement Moreover, in the same patient the dilatation of the arterioles and the prolongation of the electrical systole disappear promptly, the edema, decreased vital capacity and elevated venous pressures disappear more slowly, while the dilated heart and abnormal electrocardiographic complexes return to normal only after several weeks of treatment These variations in rate of improvement indicate that in man primary vitamin B_1 deficiency, when chronic, is followed by secondary changes of slow reversibility The gross and microscopic studies of the heart corroborate this contention Cardiac dilatation and, occasionally, hypertrophy, "hydropic" degeneration of the myocardial fibers and increase in intercellular substance (collagen) are evidences of myocardial damage That these do not represent simply "myocardial edema" is shown by the unaltered water content of the myocardium Such a transition from chemical disturbances to physiological and ultimately to structural changes is not peculiar to the cardiovascular system in vitamin B_1 deficiency Changes of a similar nature occur in the central and peripheral nervous systems and probably also in other organs They are comparable to the disturbed functions and lesions of the nervous system, intestinal tract and skin in pellagra, and of the spinal cord in pernicious anemia

Clinical and Therapeutic Implications in the Cardiovascular Dysfunctions Associated with Vitamin Deficiencies The therapeutic indications for patients with definite vitamin deficiency are obvious They should receive a well-balanced diet of adequate caloric value, rich in vitamin "B" In resistant or severe cases the parenteral administration of pure vitamin

B₁ or its extracts is indicated because such patients often suffer from anorexia with constipation or with diarrhea, and consequently have not only a low intake but also an impaired utilization of food.

It is well to bear in mind that patients with chronic organic heart disease may have, in addition, cardiovascular disturbances related to avitaminosis. The nutrition of patients with chronic heart disease, especially with congestive failure, is frequently poor. It is particularly important to give such patients a balanced diet rich in vitamins.

The doses of crystalline B₁ administered were larger than those indicated by experimental evidence. Such large doses were given mainly because there is available no clinical test which could be used as a guide for the adequacy of the dosage. It is of interest that no toxic reactions were observed, either in deficient or in non-deficient patients, following the intravenous administration of a dose as large as 50 mg. In some patients with dilated peripheral arterioles a temporary elevation of the arterial pressure followed the administration of crystalline vitamin B₁. Beneficial effects from crystalline vitamin B₁ were not observed in other diseases, including heart failure and edema, in which there was no vitamin B₁ deficiency.

Cowgill⁹ has demonstrated that the tendency to develop polyneuritis varies directly with the metabolic rate of the body, and inversely with the vitamin B (B₁) intake, hence the conditions favorable for the development of "B" avitaminosis are quite different from those associated with general starvation and inanition. Because the available evidence also strongly suggests that the cardiovascular dysfunction is closely related to, if not caused by, vitamin B (B₁) deficiencies, any condition associated with prolonged high metabolism and low intake of vitamin B₁ will be particularly liable to result in clinical avitaminosis with cardiovascular disturbances. Strenuous work, hyperthyroidism and infectious diseases with fever are such bodily states. Hyperthyroidism is usually associated with an increased appetite and with the consumption of a well-balanced diet. In rare instances, however, it may be accompanied by anorexia and persistent diarrhea, and in such cases cardiac dilatation, polyneuritis and psychosis may be present. It is interesting that Chvostek³⁶ quotes the literature up to 1917 on the association of polyneuritis with hyperthyroidism. Means³⁷ also describes suggestive cases of hyperthyroidism and vitamin "B" deficiency.

It is known, and our experience bears this out, that to patients with deficiency polyneuritis and pellagra, both of the alcoholic and of the non-alcoholic type, infections in general, and pneumonia in particular, represent grave danger. The circulation in patients with infections is comparable to that in persons performing heavy and continuous exercise. Fever per se increases the work of the heart and the rate of the circulation. It also is associated with a rise in the metabolic rate and usually with anorexia, which further accentuate a preexisting avitaminosis, as well as the associated cardiovascular dysfunctions. In a similar way the ordeal of general anes-

thesia and surgical operation may increase to the breaking point the strain on the heart and circulation of "B" avitaminotic patients

The relation of vitamin B (B_1) to infection and high metabolism explains the origin of the infectious theory of beriberi, and the occurrence of "epidemics" of beriberi. Prolonged infections, such as malaria in the tropics, will tend to aggravate the existing deficiencies, and will bring to the surface underlying or "subclinical" deficiencies. In these cases therapeutic procedures which terminate the infection or reduce the fever, together with the administration of a well-balanced diet and vitamin B concentrate or parenteral preparations, may well be life saving.

The data here presented, we appreciate, do not offer final proof of a direct relationship between cardiovascular manifestations and deficiency of vitamin B (B_1) or of any other vitamin. This problem is still open, even as far as classical "beriberi heart" of the Orient is concerned. In this study an attempt was made only to present clinical evidence on the thesis that (1) cardiovascular disturbances do occur in association with vitamin "B" types of deficiency, often with adequate or more than adequate caloric intake, (2) while the clinical picture of this condition is variable, nevertheless it is similar in several respects to that of "beriberi heart" observed in the Orient.

The observations here described also serve to demonstrate that not only pellagra, but also beriberi, occurs in Boston. This completes the picture, showing that all known types of avitaminosis attributed to the vitamin "B" group, as well as to other types of vitamins, are present in the northeastern and probably other parts of the United States.

SUMMARY AND CONCLUSIONS

1 Dysfunction of the cardiovascular system resulting from unbalanced food intake is a disease of regular occurrence in the United States. This report is based on a study of 120 such cases, 35 of which were investigated within two years.

2 The cardiovascular manifestations depend on changes in the nervous system, in the vascular system and in the myocardium.

3 Tachycardia followed by bradycardia, gallop rhythm, vagal reflex irritability, dilatation of the heart, dyspnea, orthopnea and pulmonary congestion, associated with bounding arterial pulsation, arterial "pistol" sounds, engorged veins, warm skin and edema are the usual clinical features of severe cases.

4 The hemodynamics are characterized by low vital capacity of the lungs, high venous pressure and normal arterial pressure, and by a relatively or absolutely increased velocity of blood flow and decreased peripheral utilization of arterial oxygen. The osmotic pressure of the blood is usually moderately low and frequently remains essentially unchanged while the edema disappears.

5 The electrocardiograms were normal in but 7 per cent of 67 cases. The main abnormalities consisted in changes in the T-waves and prolongation of the electrical systole (Q-T). The electrocardiographic changes in patients with pellagra or beriberi probably are due to the B₁ component of the vitamin deficiency.

6 The myocardium often showed "hydropic" degeneration of the muscle and conductive fibers and increase in the intercellular substances, but unaltered water content.

7 The cardiovascular disturbances caused by nutritional deficiencies do not form a rigid clinical syndrome. Right ventricular failure, left ventricular failure, arteriolar dilatation and increased blood flow, peripheral circulatory collapse and shock, singly or in combination, have been observed.

8 The onset of the disease may be sudden or gradual. Patients with the severe form of the disease show a tendency to fever, to bronchopneumonia and to acute fatal circulatory collapse. Under therapeutic measures such as rest, cardiac drugs, diets rich in vitamin B₁ or crystalline vitamin B₁, all the cardiovascular disturbances usually revert to normal.

9 The clinical symptoms and signs, the blood chemistry, the myocardial changes, the hemodynamics and therapeutic responses correspond to those described in "beriberi heart" in the Orient. The disease as observed in Boston, however, is characterized by more varied and more generalized involvement of the cardiovascular system.

10 Evidence is presented indicating that vitamin B₁ deficiency plays a primary rôle in the precipitation of the disease. Alcohol also is a significant factor, not only because it supplies calories without vitamin B₁, but also because its metabolic effect is similar to that of a pure carbohydrate.

11 The rate of response to vitamin B₁ in "alcoholic" and "nonalcoholic" beriberi varies. The arteriolar system shows a more rapid change than the heart. The cardiovascular disorder usually disappears before the polyneuritis. The factors influencing therapeutic responses are discussed.

12 In normal subjects, as well as in patients with diseases other than vitamin B₁ deficiency, even large doses of crystalline vitamin B₁ produce no appreciable effects.

13 The condition here described bears pertinently on the clinical behavior and the mortality rates of alcoholic and nonalcoholic patients with vitamin "B" deficiencies (beriberi and pellagra). It may explain the poor reaction of these patients to increases in metabolic rate, such as occur in febrile infections, in hyperthyroidism, or under surgical operations. The therapeutic indications under these conditions are discussed.

This study was conducted with the assistance of Dr. Florence W. Haynes and Miss Sophia M. Simmons.

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CHRONIC BILATERAL PYELONEPHRITIS ITS ORIGIN AND ITS ASSOCIATION WITH HYPERTENSION

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THE continuous study of 22 cases of chronic bilateral pyelonephritis has led to the recognition of a number of complications and accessory factors that have been found to modify the usual course of this rather common disease. In a previous publication the significant symptoms and signs of the affection were described in some detail¹. The essential characteristics of this form of pyelonephritis consist in its bilateral occurrence, usually without demonstrable or evident obstruction to the outflow of urine². It is seen most frequently in young women between the ages of 15 and 30, but may occur in children or in older women. The youngest patient in this series among adults was 15 years of age, the oldest 55. The disease is usually of long duration. Symptoms of renal insufficiency may not appear for 10 or 15 years after the infection is first initiated. In seven of our patients the disease was known to have existed for at least five years or longer, and in three of them it had been present for from 14 to 17 years. During this long period leading up to the terminal stage, which manifests itself as protracted renal failure, the symptoms are usually slight and vague. Starting with a pyelitis in childhood, an infection of the urinary tract during pregnancy or, in rare instances, an outspoken acute pyonephritis there may be from time to time attacks of unexplained fever, with or without slight or fairly severe pain in the lumbar regions. These attacks are often accompanied by the passage of cloudy urine. Occasionally there is a history of albuminuria of many years' duration. Often there is a story of malnutrition, or sometimes of retarded growth in children, leading occasionally to rickety deformities. In some instances the progress of the disease is, for years, symptomless.

Unless the patient has symptoms or signs of renal failure, the condition is usually considered to be a chronic pyelitis. It is not until headache, nausea, vomiting, loss of weight, lassitude, dyspnea, or, in a few instances, convulsions, occur that the patient, in more or less desperate condition, is seen by a physician. Thirteen of our cases were not seen until the terminal stage of the disease was far advanced. Fourteen of these patients are known to have died, and in six of them the true nature of the disease was not recognized until autopsy which was obtained in 10 of the 12 cases.

It is possible however to determine the presence of the disease years before it is so far advanced. The signs that are of particular importance

* Received for publication April 27, 1937

are as follows. There is often slight pallor, a rather dry skin, and frequently a tendency to underweight. Edema is extremely rare, except when myocardial failure complicates the later stages of the disease. Unless hypertension supervenes, the heart is not enlarged. The blood pressure is not often elevated during the early stages of the disease. The systolic blood pressure was below 125 mm and the diastolic below 85 mm of Hg in five of nine cases which were seen at this period.

As the disease advances it is usual to find that the blood pressure rises. This is not, however, an invariable occurrence, for in at least three fatal cases the blood pressure remained essentially normal. In one woman of 21 the highest recorded blood pressure was 118 systolic and 68 diastolic, in a man of 24 the blood pressure varied between 120 systolic with 78 diastolic and 145 systolic with 75 diastolic, and in a boy of 15, the highest pressure was 140 systolic and 90 diastolic.

These instances should be recorded as exceptions rather than as exemplifying the rule, for usually the blood pressure rises during the latter months or years of the disease and may reach such high figures as 225 mm of Hg systolic and 150 mm Hg diastolic.

The retina usually show no changes until the disease is far advanced or has actually reached the terminal stage.

At times there is costo-vertebral tenderness. The urine is passed in fair quantities, the specific gravity is constantly low and with the progress of the disease becomes practically fixed at a figure near 1.010 or 1.012. The urine contains traces or moderate amounts of albumin, rarely casts or red blood cells, but many leukocytes which vary in numbers from time to time. In the great majority of patients cultures from the urine give at some time a growth of *B. coli*. In a few patients this organism was constantly present, but more often it appeared only at intervals. Though the early stages of the process may not be accompanied by any definite impairment of renal function, a striking feature is the unexpected frequency with which a marked impairment of renal function occurs at a time when the patient feels perfectly well. Months or even years before the terminal stage, the non-protein nitrogen of the blood may be distinctly elevated above normal, the phthalein output greatly reduced, and the curve of excretion flattened, the specific gravity of the urine fixed at a low level, and the urea clearance far below normal. In one patient who has been under observation for 7½ years, the non-protein nitrogen of the blood has never fallen below 42 mg per 100 c.c. and has at times reached 50 mg per 100 c.c., the specific gravity of the urine has been constantly fixed between 1.001 and 1.004, the phthalein output has gradually fallen from 60 per cent to 47 per cent, and the urea clearance from 42 per cent to 21 per cent of the normal standard. During all this time the patient, except for occasional headaches and attacks of lumbar pain, has felt well and been constantly at work. In another patient the non-protein nitrogen of the blood remained about 74 mg per 100 c.c. for three years before

death, and in a third patient, who has recently died, the non-protein nitrogen of the blood has varied between 55 mg per 100 c c and 88 mg per 100 c c for three years. During this protracted period of renal insufficiency there are rarely any of the symptoms that can be ascribed to this defect.

In some of these patients who display such long periods of renal insufficiency, the urine remains neutral or slightly alkaline. This may occur in the absence of evidences of cystitis and when the urine is sterile. In such

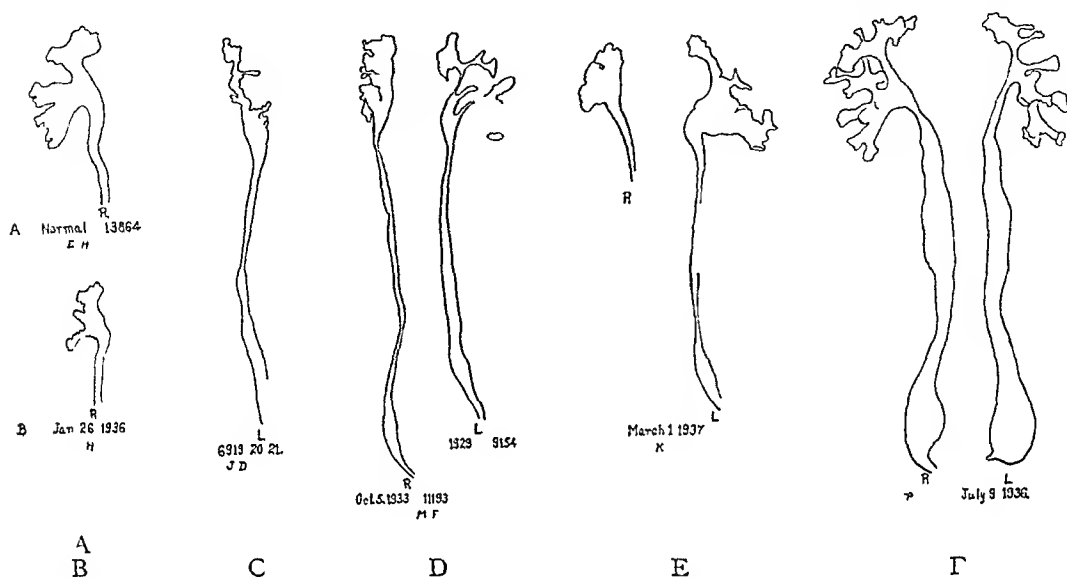


FIG 1 Case 2 (No 20 in table) Outlines of pyelograms of kidney pelves showing dilatation of ureters

- A Outline of pyelogram from right normal kidney
 - B Outline of pyelogram from right kidney Case 12 Table I
 - C Outline of pyelogram from left kidney Case 5 Table I
 - D Outlines of pyelograms from Case 1 Table I
 - E Outlines of pyelograms from Case 1 text (Case 18 Table I)
 - F Outlines of pyelograms from Case 2 text (Case 20 Table I)
- Showing marked dilatation of ureters and pelves

patients it may, in fact, be impossible to produce an acid urine, either by the administration of ammonium chloride or by a ketogenic diet. This occurred in one of our patients who developed symptoms of acidosis, with a reduction of the CO_2 combining power of the serum to 29.6 volumes per cent, and still excreted urine which was alkaline or neutral in reaction.

One of the most important evidences of the disease is obtained by pyelography. The characteristic change observed in the pyelogram is a distortion, flattening and reduction in the size of the pelves (figure 1). This may occur without dilatation of the ureters, though in some instances there may be uniform or irregular dilatation of the ureters. An actual enlargement of the pelves of the kidneys is rare. The cystoscopic examination shows, as a rule, no changes in the bladder, though in one case ulceration of the mucosa was observed.

A combination of these various features produces a clinical picture which has such distinctive characters that one is usually able to recognize the disease, even though it occurs in patients who are apparently in excellent health.

The pathological changes in the kidneys which have been so frequently described^{3, 4, 5, 6} suggest that the progress of the disease is caused through the gradual destruction and elimination by inflammation and searing of small portions of the kidneys. The intervening parenchyma remains comparatively normal in appearance and apparently functions adequately. The kidney fails completely when this process of amputation reaches a point that is incompatible with life, or when a complication such as arteriolar sclerosis, or acute diffuse glomerular nephritis, is superimposed upon the renal structure that is already seriously damaged. Death may also occur from some intercurrent infection, but in all of our fatal cases uremia closed the picture.

It is of great importance to determine the exact manner in which the disease arises. In the majority of cases cultures of the urine and from the pelves of the kidney show a growth of *Bacillus coli*, and it is to be presumed this organism causes the original and the persistent infection. A gross inflammation of the mucous membranes of the bladder, such as commonly occurs in strictures of the urethra or prostatic hypertrophy is not present. There is rarely any evidence of gross strictures of the ureters though in cases of long duration points of narrowing, particularly in the portion that courses through the wall of the urinary bladder, may be present. It is in these cases that irregular dilatation of the ureters may be found. It is extremely difficult to determine, once the disease is well established, whether these anatomical strictures originally predisposed to an ascending infection of the urinary tract, or simply occur as a complication of the long continued passage of infected urine from the kidney. There is, however, considerable evidence to indicate that in infants and young children, so-called pyelitis is actually an acute pyonephritis, arising bilaterally from hematogenous infection of the kidneys. (Bugbee,⁷ Chown,⁸ Wilson and Schloss,⁹ Band, Dunlop, and Dick¹⁰)

It is very difficult to obtain definite information on this point in the adult, but the following cases seem to indicate that acute pyonephritis may occur in adults as a primary disease presumably from hematogenous infection of the kidneys by *Bacillus coli*, and further that recovery from the acute phase may be followed by intermittent pyuria due to *Bacillus coli*. The first case must exemplify a very unusual situation.

Case 1 (No. 18 in table). A young unmarried white girl, 16 years of age, was admitted to the Johns Hopkins Hospital on September 27, 1936, complaining of cramps in the stomach and dysentery. Her father had died of cancer of the rectum. For seven or eight years she has been subject to attacks of abdominal cramps which have come on every few months. They have lasted two to three days. Eight days before admission she had one of these attacks which was very severe. Three days after the onset of this attack her eyes had become swollen, and a day or two later her hands and feet were also swollen.

Physical examination showed a pale undernourished girl with temperature 100.6°, pulse 116, respirations 18. There was moderate anasarca, with swelling of face and pitting over shins. The fundi oculi showed increased shimmer of retina. Lungs were clear to percussion and auscultation. Heart was not enlarged and there were no murmurs. Blood pressure was 120 systolic and 85 diastolic. Abdomen was distended and tender. Liver, spleen, and kidneys were not palpable. Slight clubbing of the fingers was noted. Red blood cells 1,870,000, hemoglobin 39 per cent, white blood cells, 8,520, polymorphonuclear leukocytes, 60 per cent. Urine was acid, 1.010 specific gravity, there were large amounts of albumin—7 grams per liter, many granular and leukocytic casts, few red blood cells and great numbers of leukocytes. September 28, non-protein nitrogen of blood was 80 mg per cent, total plasma proteins 4.81 gm per cent, albumin globulin ratio 60/40. Blood culture made September 29 showed no growth. Culture of urine on September 30 showed growth of *Bacillus coli*. On this day a transfusion was given. October 2, phthalein excretion was 12 per cent in two hours, October 3, phthalein excretion was 24 per cent in two hours. Temperature remained elevated from September 27 to October 17. She continued to have severe abdominal cramps and diarrhea. On October 5, the non-protein nitrogen of blood was 76 mg per cent, and urea clearance 25 per cent of normal standard.

After October 5, there was some improvement. The edema diminished and finally disappeared by October 11. The albumin decreased to a small amount by October 9, but casts, red blood cells, and leukocytes continued in large numbers in the urine. There was rapid improvement in renal efficiency. By October 12 the non-protein nitrogen of the blood had decreased to 34 mg per cent, and on October 13, the phthalein was 72 per cent in two hours. By October 15 the non-protein nitrogen of the blood was 30 mg, and the urea clearance 64 per cent of maximum standard. Cultures from the urine continued to show heavy growth of *Bacillus coli*. At this time proctoscopic examination showed great numbers of polyps in the rectum and roentgen-ray of the colon demonstrated multiple polyposis, which was believed to explain the attacks of abdominal cramps and diarrhea that she had had for many years.

She was given ammonium chloride for a few days until the urine became sufficiently acid (pH 5.5), and, on October 18, 12 gm ammonium mandelate were administered daily for five days. By October 22 cultures of the urine showed no growth of *Bacillus coli*. Subsequently cultures from October 27 to November 2 were sterile. The albumin, red blood cells, and leukocytes rapidly diminished in the urine. For a few days the casts increased. November 2 to 6 the urine contained either traces of albumin or no albumin, occasional leukocytes, no red blood cells, and occasional hyaline casts. On November 29 the phthalein was 93 per cent. November 10 Hemoglobin 80 per cent, red blood cells 4,070,000. Since this time, as the chart (chart 1) shows, there have been recurrences of the bacilluria, controlled temporarily by the use of ammonium mandelate. Pyelograms made in March 1937 showed no abnormalities (figure 1 E).

It seems evident that this girl was suffering from an acute pyonephritis due to *Bacillus coli*. The renal infection was possibly hematogenous and secondary to an inflammation of the colon associated with multiple polyposis. Rapid sterilization of the urine and complete recovery from the acute pyonephritis followed the administration of ammonium mandelate, but subsequent cultures from the urine have given at intervals a growth of *Bacillus coli* indicating that the infection of the kidneys has not been eradicated. This patient not only illustrates one mode of origin of chronic pyelonephritis, but exemplifies in a striking manner the immediate benefit derived from the

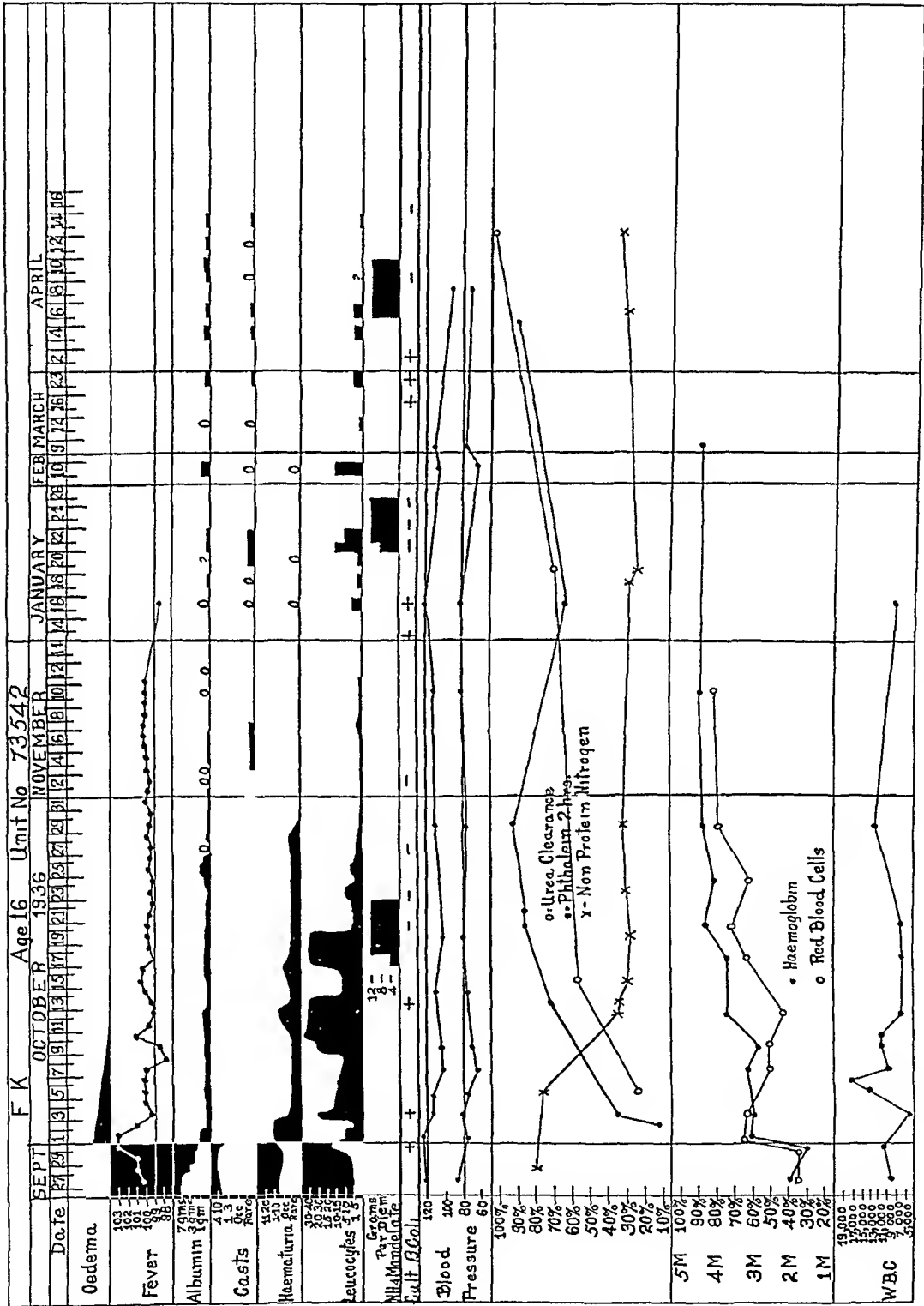


CHART 1 (Case 1 text) showing course of illness of F.K. from September 1936 to April 1937

use of ammonium mandelate in infections of the urinary tract by *Bacillus coli*

Though it seems probable that this mode of onset may account for the origin of the disease in many, if not the majority of cases of this type of bilateral pyelonephritis, it is quite possible that some form of obstruction to both ureters may predispose the kidneys to infection. The enlarged uterus of pregnancy might act in this manner. In rare instances, congenital stricture or unexplained bilateral dilatation of the ureters, such as has been described by Ellis and Evans,¹¹ might produce the same result. The following case may be an example of this latter condition.

Case 2 (No 20 in Table) A white married man, 29 years of age, was admitted to the Urological Service of the Johns Hopkins Hospital on June 24, 1936 (For the early records I am indebted to Dr H H Young.) He complained of "kidney pain." He came of a healthy family and had usually been well. He could not recall any past illnesses except measles and mumps as a child. There had been no urinary disturbances. Married eight years, his wife had had no miscarriages, he denied any venereal infection. While in perfect health he suddenly developed pain in the epigastrium and both kidney regions nine weeks before admission (May 1936). The attacks were repeated but did not prevent his working. He soon developed jaundice, lost appetite, was nauseated and vomited. Jaundice lasted about two weeks and as it disappeared he improved, but attacks of pain persisted. Two weeks before admission (about June 10, 1936) pains became particularly severe, his temperature rose to 103° and he went to bed. Nocturia appeared without dysuria. He had chills and fever, and the pain became worse.

On admission his temperature was 102° F, blood pressure 195 systolic and 112 diastolic, pulse 72. He was somewhat undernourished. There was no edema. Lungs were clear to percussion and auscultation, the heart was not enlarged, the PMI was 7.5 cm to left of midline in the fourth interspace. There were no murmurs. There was tenderness in the costo-vertebral angles, over the kidneys, and to the left and below the umbilicus. Liver edge was readily palpable, spleen not felt. The prostate was small and not tender. Hemoglobin was 94 per cent, leukocytes 12,500. The urine was acid, amber, sp gr 1.020, no sugar, albumin 2+, no casts, rare red blood cells. Wassermann reaction was positive. On June 25, phthalein excretion was 89 per cent, non-protein nitrogen of the blood 60 mg per 100 cc. Culture of the blood showed less than one colony per cc of *Bacillus coli*, culture of the urine showed *Bacillus coli*.

An irregular temperature persisted with continuation of the pain. By June 26 blood pressure had fallen to 128 systolic and 70 diastolic, blood urea 32 mg per 100 cc. The urine continued to show small amounts of albumin and pus, but only occasional casts. Blood cultures made on July 1, 3, and 5 showed no growth. Cystoscopic examination showed no abnormality of the bladder, the ureters could be readily catheterized, cultures of urine from both ureters showed *Bacillus coli*. Phthalein appeared in the urine from both ureters in five minutes, 25 per cent was excreted from the left and 35 per cent from the right in 30 minutes. Ureteral catheters were left in place. There was excellent drainage from both sides, but the patient continued to have chills and fever. Retrograde pyelograms on July 9 showed marked dilatation of the lower portions of both ureters with pelvis that appeared normal (figure 1 F). There were no calculi.

He was admitted to the Medical Wards on July 12, 1936. At this time the blood pressure was 120 systolic and 72 diastolic, he showed loss of weight and some anemia.

The hemoglobin was 76 per cent, red blood cells 3,600,000, but there was no increase in leukocytes, 8,000. There was still fever, and there was tenderness to deep pressure in both flanks. The urine was alkaline, sp. gr. 1.001, with traces of albumin and much pus, but no casts. There was fever with daily rises of temperature from 99.4° to 102.4°.

On July 13 the non-protein nitrogen was 25 mg. per 100 c.c., the CO₂ combining power of the serum 65.3 per cent, and a culture from the urine showed heavy growth of *Bacillus coli*. A culture from the blood gave no growth. The patient was placed on 3 grams of potassium iodide a day, and seven days later the temperature was lower, the fever disappearing after the twelfth day. He was discharged on July 29, 1936, but returned to the hospital on November 13, 1936, saying that he had received eight injections of arsphenamine and eight injections of bisinuth in the interval. He had felt well, working daily until three days before admission (November 10), when he experienced dull pain in the lumbar region and in the epigastrium, and felt chilly. The pain grew worse and he had chills, fever, sweats, and frequency of urination. On admission the temperature was 104°, pulse 92. The skin was dry, the lungs clear, the heart not abnormal, and the blood pressure 120 systolic and 60 diastolic. There was tenderness in the costo-vertebral angles and in both lumbar regions, the liver was palpable, the spleen not felt. There was no edema. The hemoglobin was 100 per cent, red blood cells 4,700,000, leukocytes 12,750. Urine was cloudy, pale, sp. gr. 1.007, acid, showed no albumin, no casts, but great numbers of leukocytes, cultures gave a heavy growth of *Bacillus coli*. November 14, non-protein nitrogen of the blood was 30 mg. per 100 c.c. November 15 phthalein excretion was 70 per cent in two hours. November 18, urea clearance was 68 per cent of normal standard. By November 17 temperature had fallen precipitately to normal, and traces of albumin and much pus appeared in the urine. In an effort to combat the urinary infection after a preliminary course of ammonium chloride (6 to 8 grams a day) from November 15 to November 21, when the required urinary acidity of at least pH 5.5 was obtained, ammonium mandelate was administered in doses of 12 grams a day from November 21 for 14 days without definite effect, for *Bacillus coli* was cultivated persistently from the urine from November 14 to December 9, five days after the course of ammonium mandelate. There was, however, gradual symptomatic improvement. On December 1, 1936, the non-protein nitrogen of the blood was 32 mg. per 100 c.c., the blood pressure 130 systolic and 80 diastolic, and on December 6 the phthalein excretion was 50 per cent in two hours. On December 10 cystoscopy showed a granular cystitis, the ureters could be readily catheterized, the ureteral orifices were dilated by bougie. Pyelograms made again on December 10 were similar to those obtained on July 9 and showed no abnormality of the pelves, but a dilatation of the ureters affecting particularly the lower portions (figure 1 F). On January 2, non-protein nitrogen of the blood was 32 mg. per 100 c.c. January 4, cultures from urine again showed *Bacillus coli*. Following a preliminary period of ammonium chloride a second course of ammonium mandelate was started on January 5, but this could not be completed for the patient left the hospital on January 9, 1937.

It seems more than probable that this case is illustrative of an acute pyonephritis arising from an hematogenous infection by *Bacillus coli* in a patient who was already the subject of an abnormality of the urinary tract consisting of bilateral dilatation of the ureters due perhaps to some congenital anomaly. It is impossible, however, to exclude the urinary tract as the primary seat of infection with an invasion of the blood subsequently by *Bacillus coli*.

The acute illness in this patient may be regarded as the onset of a serious

and perhaps progressive infection of the kidneys and renal pelves, for it has not, so far, been possible to eradicate the infecting organism

It has been pointed out that as the bilateral chronic pyelonephritis progresses there is a distinct tendency for the blood pressure to rise. The blood pressure was above 160 systolic and 105 diastolic in 10 of 15 patients who were observed during the advancing or terminal stages of the disease. In half of these the systolic pressure was 200 or over, and in 10 the diastolic pressure was between 110 and 150 mm of Hg. The gradual rise of blood pressure from comparatively normal levels (105/60 and 146/90), during the early stages, to high levels (200/118 and 162/102) in the later stages could actually be followed in two patients.

On the other hand, in seven cases, including the two patients referred to above who were observed during a comparatively early stage of the disease, only one showed a systolic blood pressure over 140 or a diastolic blood pressure over 85 (146/90). The highest systolic pressure in five of these patients was not above 120, or the diastolic pressure above 85, while in four the highest diastolic pressure was not above 80 mm of Hg. In one patient the highest blood pressure was 138 systolic and 78 diastolic.

Since the hypertension comes as one of the late manifestations of the disease, it is important to learn whether it is due to a complicating arteriolar disease or whether it is to be considered as an essential part of the clinical picture and is related directly to the failing renal function itself.

It is hardly possible to accept the latter suggestion without some reservations, for it was found that the blood pressure was within normal limits or only slightly increased in seven patients in whom the evidences of renal failure were pronounced as measured by the retention of non-protein nitrogen, the excretion of phthalein, or the urea clearance. Five of these patients died. In four the systolic pressure never rose above 145, and in one varied between 110 and 170. One patient is living and the fate of the other is unknown. Four of the fatal cases came to autopsy.

On the other hand, if one inquires into the combination of hypertension with hemorrhagic retinitis and arteriolar lesions of the fundus, it is found that the relationship is quite striking. Table 1 gives the results of this study. Dr. Arnold Rich has very kindly examined the organs of the cases that have come to autopsy, with special reference to the condition of the arterioles. It has, therefore, been possible to add the valuable information obtained from him to the study of Cases 5, 6, 7, 8, 9, 11, 15, and 16 (table 1).

It may be seen that in 11 of the 12 patients who showed any elevation of blood pressure above normal, pathological lesions in the arteries and arterioles of the retina were observed during life in all but one. The arteriolar disease was combined with hemorrhages in eight cases and with hemorrhages and exudates in four patients. On the other hand, in seven cases seen during the early stages of the disease when the blood pressure was

TABLE I

No	Sex	Age	Duration	Blood Pressure	NPN mg %	Urea Clearance cc Normal	Retinal Lesions				Living	Dead	Autopsy				Remarks
							Arterio- sclerosis	Edema Disks	Hemor- rhages	Fundus			Pyelo- nephritis	Arterio- sclerosis	Glomer- ular Nephritis		
1	I	34	7 yrs	146/92	50	21	++	0	+	0	+						
2	I	26	7 yrs	105/60-200/118	128	6	++	0	0	++	+						No autopsy
3	M	19	16 yrs	120/70-140/70	140	9	0	±	0	0	?						
4	F	21	7 mos ?	110/60-118/68	70	7	++	±	+++	0		+					No autopsy
5	I	18	14 yrs	175/135-225/150	130	3	+++	++	+++	+++	+	+++	±	0			
6	M	21	9 mos ?	120/78-145/75	312	2	0	0	0	0		+	+++	0	0		
7	I	28	3 weeks?	160/90-170/110	250		++	+	+	0		+	+++	+	0		
8	F	15	3 yrs +	110/60-120/80	168-244		0	0	0	0		+	+++	0	0		
9	F	36	17 yrs	160/100-230/140	40	40	++	±	0	0		+	+++	+	0		
10	M	23	?	116/70-110/75	46	52	0	0	0	0	+						Early
11	F	37	4 mos +	200/110	170		±	0	0	0		+	+++	±	+++		
12	F	22	?	140/80-180/120	116	5	±	+	++	++		+					No autopsy
13	F	52	1 yr +	138/90-170/110	220	45	±	0	0	0		+					No autopsy
14	M	15	3 yrs +	140/90	301		±	±	+	0		+	?	0	+++		
15	F	26	7 yrs	162/112-226/108	112	135	±	+	++	++		+	++	+	+++		
16	F	55	3 mos ?	110/80-170/110	96		±	±	+	0		+	+++	0	0		
17	F	58	?	165/80-206/110	55-88							+					Hyperparathyroidism no autopsy
18	F	16	5 days	120/80	80-32	25-70	0	0	0	0	+						Acute
19	M	45		155/100	90-50		0	0	0	0							Hyperparathyroid
20	M	29	8 mos	120/60	30	68	0	0	0	0	+						Early
21	F	44	4 yrs ?	94/60-110/85	34-53	49-42	0	0	0	0	+						
22	M	23	?	135/78	60	355	0	0	0	0	+						

within normal limits, except in one patient when it was 140 systolic and 85 diastolic, the fundi were normal. In this one patient slight alterations were observed in the arterioles. In spite of the normal blood pressure and the normal appearance of the fundi oculi, the renal function was definitely impaired in four. In the seven patients seen during the latter stages of the disease, in whom the blood pressure was either within normal limits or only slightly elevated but in whom the renal function was markedly depressed, pathological changes were seen in the fundus in only three, in two of whom the pressure was slightly elevated.

It seems, therefore, that the ophthalmological picture of retinal arteriolar sclerosis and hemorrhagic retinitis is much more nearly related in these patients to the hypertension than to the presence or degree of renal insufficiency.

The results of the microscopical examinations of the organs at autopsy are as follows. All cases showed a marked and extensive pyelonephritis. In

no case, however, could Dr Rich find, in addition to the pyelonephritis, pronounced or extensive hyaline sclerosis of the arterioles of the kidneys or other organs such as the pancreas, adrenals, and intestines

In the four fatal cases (6, 8, 14, and 16) in which the blood pressure remained within normal limits or was only slightly elevated, sometimes only at intervals, the arterioles of the kidney, pancreas, adrenals and intestines appeared normal. In one case (14) there was a complicating and definite glomerular nephritis. In three cases in which hypertension was marked and was one of the outstanding features of the clinical course a few arterioles were found in the kidney, pancreas, adrenals and intestines which showed moderate hyaline sclerosis, but the lesions were almost minimal in extent. One of these patients showed extensive hemorrhagic retinitis with retinal exudates (Case 5, fundi). A second showed extensive hemorrhagic retinitis with pronounced lesions in the arterioles and the third presented well marked changes in the retinal arterioles, without hemorrhages, exudates or edema. Two patients (11 and 15), both with pronounced hypertension, showed in addition to the extensive pyelonephritis a diffuse and advanced glomerular nephritis with moderate to minimal hyaline sclerosis of the arterioles in the kidney, pancreas, and adrenals. One of these patients (11) was not observed to have retinitis though the retinal arteries showed abnormalities, the other (15) showed marked lesions of the retinal arterioles with fairly extensive terminal hemorrhagic and exudative retinitis.

One must conclude from a study of this short series of fatal cases that widespread and extensive arteriolar sclerosis did not occur. Scattered and sometimes minimal hyaline sclerosis of the arterioles of the kidney, pancreas and adrenal was found in five of the fatal cases who during life had markedly elevated blood pressures. In two of these cases there proved to be, in addition, a diffuse chronic glomerular nephritis. In the four cases in which hyaline sclerosis of the arterioles was not seen in sections of the organs, the blood pressure during life was within normal limits in one and only slightly elevated in the others. In one of these latter cases a diffuse chronic glomerular nephritis was found at autopsy (14).

It appears, therefore, that the hypertension which was found to exist in the terminal stages of the disease, or was observed to develop during the course of the disease in two patients, was not associated with pronounced arteriosclerosis of the vessels of the kidneys, or with widespread uniform involvement of the arterioles of other organs. In spite of the marked hypertension and the lesions in the fundi, which were present during life in several of these patients, the pathological lesions at autopsy were not as extensive as those usually observed in arteriosclerosis. Unfortunately the fundi were only examined histologically in one case. In this patient (Case 5) the blood pressure varied from 180 systolic and 150 diastolic to 225 systolic and 150 diastolic, there was cardiac hypertrophy with myocardial insufficiency as a terminal event. It was noted by the late Dr William H Wilmer that

the optic discs were swollen, the arteries narrow, tortuous and irregular, and that there were many hemorrhages and exudates in the choroid. The picture was considered by him to represent vascular sclerosis of the retinal and choroidal vessels. This histological examination of the retina was made of several sections cut at different levels through both orbits. They showed that there was edema of the nerve head with several hyaline arterioles in the nerve head. There were no hyaline arterioles in the retina, no hemorrhages or exudates, but several small scars which may have been the result of organized hemorrhages or exudates. Such marked incompatibilities are certainly not usual, and it is difficult to understand why abnormalities during life, which are, as a rule associated with arteriosclerosis should prove, at autopsy, to be accompanied with so few anatomical lesions.

Unfortunately lumbar puncture was not performed in these patients and no information is available, therefore, concerning the pressures in the spinal fluid. In view of Pickering's¹² observations upon the association of albuminuric retinitis with high spinal fluid pressures, it would have been valuable to have data upon this point.

It was often noted that the height of both the systolic and diastolic blood pressures changed considerably from time to time in many of these patients. In Case 9 there were variations from 160/100 to 230/140, in Case 12 from 140/80 to 180/120, in Case 13 from 138/90 to 170/110, and in Case 16 from 110/80 to 170/110. Although this is not uncommon in some instances of arteriosclerosis it is observed more often in patients who are suffering from the form of hypertension generally designated as essential. It is also to be remarked that retinal hemorrhages were much more common (8 cases) than exudates (4 cases), and that swelling of the optic disc, though frequent (9 cases), was rarely marked.

One might therefore conceive of the condition as being somewhat different from the classical forms of arteriolar disease. Although it is impossible to correlate satisfactorily the elevation of blood pressure with the presence or intensity of renal insufficiency, it is to be noted that retinal hemorrhages and exudates were only found in those patients who showed evidences of marked renal impairment.

The experimental work of Goldblatt and his coworkers¹³ has shown that ischemia of the renal tissues of dogs and monkeys¹⁴ produced by reducing the arterial flow of blood to the kidney through constriction of the renal arteries, results in a persistent elevation of blood pressure. Even constriction of the arterial flow to one kidney may, and usually does, result in a definite increase in blood pressure, though the rise is much greater and of longer duration when both renal arteries are constricted.

This work has been amply confirmed by Page,¹⁵ Elaut¹⁶ and by Wood and Cash.¹⁷ Page has shown that denervation of the pedicle of the kidneys does not prevent the rise of blood pressure following the Goldblatt operation, and Goldblatt¹³ reports that excision of the dorsal sympathetic ganglia and splanchnic nerves does not reduce the blood pressure in his dogs.

The experiments of Tigeistedt and Bergman¹⁸ upon the presence of a pressor substance in the kidneys of rabbits designated by them "Renin" have been repeated and modified by Harrison, Blalock, and Mason,¹⁹ and by Prinzmetal and Friedman²⁰. The former authors found that extracts of the kidneys of normal dogs usually produced moderate transient increases in blood pressure when injected intravenously into unanesthetized dogs, but that extracts of kidneys from dogs made hypertensive either by ligation of the ureters or by the Goldblatt method produced a much greater rise in pressure than the extracts from normal kidneys. Prinzmetal and Friedman not only compared the extracts from the two kidneys of dogs, after one renal artery had been constricted with resulting hypertension, but compared the effects of extracts from the kidneys of patients who had died with benign and malignant hypertension, chronic glomerular nephritis, and from chronic pyelonephritis with extracts of normal human kidneys. It was found that the extracts of the abnormal kidneys from both dogs and human beings were usually much more potent in their ability to raise the blood pressure when injected intravenously into dogs than the extracts of normal kidneys.

It is not understood how renal ischemia or the injection of extracts of diseased kidneys cause hypertension, but the results suggest that the pressor substance present normally in the extract from the cortex of the healthy kidney is much increased in the diseased kidney. Whether these experiments and observations have any bearing on the hypertension developing during the later stages of chronic pyelonephritis with contracted kidney it is not possible to say, but there are analogies which are highly suggestive in the two sets of conditions.

It is a matter of particular interest that constriction of only one renal artery in dogs will result in a moderate degree of hypertension which may persist for some time. Both Jacoby⁵ and Haslinger⁴ report instances of unilateral "Schlumpfiere" due to chronic pyelonephritis and the condition does not seem to be extremely rare. It may occur in individuals in whom a chronic infection of the kidney occurs in relation to a renal calculus imbedded in one of the calyces of the kidneys. One such case has come under my observation. In this patient the unilateral pyelonephritis was associated with hypertension. The blood pressure varied from 210/120 to 140/100. There was no evidence of renal insufficiency for the phthalein excretion was 90 per cent in two hours, the non-protein nitrogen of the blood 30 mg per cent, the urea clearance 63 per cent of the normal standard, while the specific gravity of the urine varied from 1.006 to 1.030. The question naturally arises, however, as to whether disease, such as this, of one kidney could produce a persistent elevation of blood pressure in man.

CONCLUSIONS

The contracted kidney of chronic pyelonephritis may arise in adults, as it is said to arise in infants and children, from a hematogenous infection of

the kidneys. The bacterium which is usually responsible for this infection is *Bacillus coli*.

The onset of the disease may assume the form of acute pyonephritis.

The disease progresses insidiously for years but may be recognized in many patients during this insidious stage by special methods of examination.

During the latter phases, the chronic renal insufficiency is often, but not always, combined with intermittent or persistent hypertension.

Hemorrhagic retinitis occasionally with exudates may occur at this time.

The hypertension was not associated with pronounced or extensive arteriosclerosis in nine fatal cases which came to autopsy, for among six of these patients who had an elevated blood pressure during life only five showed any arteriosclerosis at autopsy, and in two of these it was minimal in degree and in extent. In three of the fatal cases the chronic pyelonephritis was combined with a chronic diffuse glomerular nephritis.

The explanation for the hypertension occurring particularly during the latter stages of the contracted kidney of pyelonephritis is not clear.

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PRIMARY INFLAMMATION OF ARTERIES

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ARTERIES may become inflamed because of the extension of neighboring inflammations or because of the action of bacteria or parasites brought to the site from some more or less remote portal of entry. The disease is due to the presence of the infective agents and their products. There are other forms of arteritis which appear to be independent of the immediate presence of infectious organisms. Ultimately both these forms of arteritis are probably due to the products of the organisms, but there is at least an academic difference between those in which bacteria are found in the inflamed focus and those in which they are not. Similar lesions are found without known infection in the body. Furthermore, there are some in which hyperergic phenomena seem to play an important part. It is proposed to apply the term secondary arteritis to those in which infective agents are present and the term primary arteritis to those in which these agents are not demonstrable.

Vascular changes in acute infectious diseases have been extensively studied and much of the pertinent literature is reviewed by Karsner and Bayless. Degenerative and mild or severe inflammatory lesions of the arteries, not directly caused by an infective agent, are well known, but few if any correlative studies have been published. The original account of periarteritis nodosa by Rokitsansky in 1852, correlated with the clinical aspects by Kussmaul and Meier in 1866, has been followed by many publications on arterial inflammations, in which the term has been employed to designate several varieties of necrotizing and exudative arteritis. Critical examination of several reports shows that what is called periarteritis nodosa by the authors does not fit even the imperfectly known clinical or pathological characters of the disease. The confusion is recognized by Klinger, Arkin and others who have suggested distinguishing features. This report is a further attempt at clarification. The arterial diseases described below have been found sometimes in single organs or parts, sometimes in a few separate situations and sometimes widely distributed. In this study attention is directed particularly to small arteries of different size, generally with an outside diameter of something in the order of 100 to 500 micra and not

* Reported in abstract before the meeting of The American Association of Pathologists and Bacteriologists, April 10, 1936 (*Am. Jr. Path.*, 1936, **xii**, 740).

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Aided by a grant from the Josiah Macy, Jr. Foundation.

† In the literature the terms necrosing and necrotizing are used interchangeably. The latter has become customary in this laboratory.

including arterioles with an outside diameter of 50 micra or less. The inflammations occupy usually only a comparatively short segment of the vessel. They do not frequently extend to the arterioles and if they do, they involve only the proximal part of the arteriole.

In order to facilitate discussion, a classification is desirable and the following scheme is suggested:

ARTERITIS

Acute

Alterative (degenerative)

Necrotizing

Exudative

Vegetative (thrombo-arteritis)

Proliferative

Organizing

Chronic—combinations of

Intimal

Medial

Adventitial

Acute Alterative (Degenerative) Arteritis. The simpler retrogressive changes are found principally in the form of intracellular and intercellular edema. Lesions of this sort were described as early as 1869 by Hayem as an accompaniment of infectious diseases. The intima may show swelling not only of the endothelial lining cells but also those of the sub-endothelial



FIG. 1. Edema of media, observed as a vacuole at one pole of section, together with granularity of cytoplasm and almost complete disappearance of medial nuclei. Acute degeneration. Male, aged 5 years, rheumatic fever. ($\times 500$)

tissues in arteries of sufficient size to have this layer. Intercellular accumulations are not frequent but may be observed, especially in rheumatic fever. The media may show the same forms of disease. So-called *chromotropic* degeneration is found much more often in the media than in the intima. It differs from simple edema in that it stains somewhat as does connective tissue mucoid, but is probably primarily edematous in character. Changes in the elastic laminae include swelling, splitting and fragmentation. The justification for regarding these degenerative lesions as inflammatory lies not in the fact that they invariably show associated exudative or proliferative phenomena, but rather in that they exhibit these changes as the disease progresses. This progression is indicated by comparison of a large number of specimens rather than by directly observed sequences.

In addition to the infectious diseases, vascular edema has been observed in neo-arsphenamine poisoning (Christianson), in experimental allergy (Murasawa, and Kaiserling and Ochse) following partial denervation (Kerper and Collier), as the result of repeated grafting of adrenals (Leriche and Froehlich), and as a result of prolonged life in compressed air (Smith, et al). Both edema and chromotropic change are common in *periarteritis nodosa*.



FIG. 2. Acute necrotizing arteritis in kidney. Unexplained acute diffuse arterial disease. Female, aged 19 years. ($\times 194$)

Acute Necrotizing Arteritis Except where a lesion is found in arteries which are so small that they approach arteriolar size, necrosis generally is first seen in the media. It may occur as an isolated area but usually involves the entire circumference of the artery in a given segment. Confluence of cells, coarse granularity or hyalinization of cytoplasm and complete dis-

appearance of nuclei usually characterize the necrosis. With the exception of minute arteries, pyknosis and karyorrhexis are only occasionally present. Necrosis often extends to involve the intima and adventitia, but except for the smallest arteries is rarely primary in those coats. In contrast to the simpler degenerative lesions, exudation is constant when necrosis is found. The proportions of the cells of the exudate vary, sometimes they are principally lymphocytes and sometimes the polymorphonuclear leukocytes predominate. Lesions of this sort are observed in experimental anaphylaxis or allergic states (Kaiserling and Ochse, Ssolowjew and Ariel, Eickhoff), as the result of injections of trypan blue (Pfuhl), following injections of specific antisera (Matsugi et al), in the Schwartzman phenomenon (Karsner and Moritz), following injections of allylamine (Mellon, Baker and McElroy), and other procedures. In man the necrotizing lesions are occasionally found in infectious diseases, especially those with septicemia, they occur in rheumatic fever and are well shown in the skin of erythema induratum.

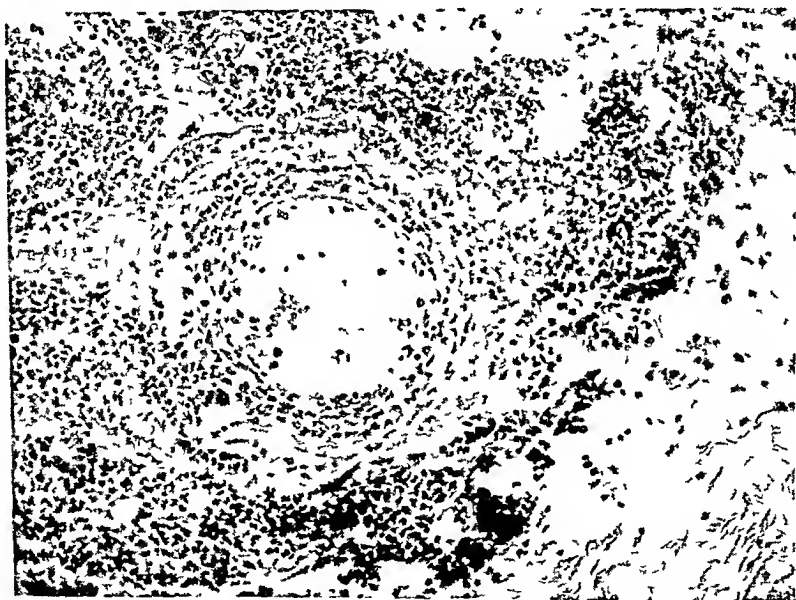


FIG 3 Acute exudative arteritis, with hemorrhage. Erythema induratum. Female, aged 19 years. ($\times 194$)

Acute Exudative Arteritis The term exudative includes both cellular and fluid exudation. The fluid can be determined to be exudative anatomically only by the presence of fibrin. Cellular exudation may be present without deposition of fibrin and if both be present the cellular component predominates, but occasionally the fibrin may form a conspicuous part of the exudate. Lesions of this sort are found especially in secondary arteritis, but are not infrequent among the primary forms. Exudation accompanies other changes such as degeneration, necrosis and cellular pro-

liferation. It occurs in a wide variety of conditions including some of the cases of rheumatic fever. The combination of necrosis and exudation, a necrotizing-exudative arteritis, characterizes the acute stages of periarteritis nodosa and occurs in the conditions noted in the preceding paragraph.

Acute Vegetative (Thrombo-) Arteritis. Although it may be true, as claimed by Nygaard and Brown, that thrombosis can occur without disease of the intima or other coats of the vessel, the deposit of thrombi usually follows other arterial lesions. Thrombosis is common to the more severe arterial inflammations and also occurs in arteries where the inflammation



FIG. 4. Acute vegetative arteritis. Thrombus attached to wall of a large coronary artery. No bacteria. Male, aged 24 years. Rheumatic fever. ($\times 226$)

or degeneration can be identified anatomically only as the result of careful study. The deposit of fibrin may start in the intima or upon the intima and may be of focal form, resembling vegetations, or occlusive. Other phenomena of inflammation are frequently found. The resemblance of this form of arterial disease to endocarditis has been emphasized by Baehr, Gross, Bender, Matsugi and others. It would appear that in the arteries as in the endocardium, the primary lesion is subintimal and the thrombus formation secondary. In those cases in which endocardial disease is present, there may be emboli into the arteries, but thrombo-arteritis occurs without associated endocarditis and can be considered to be an independent phenomenon. In some instances it may be due to deposit of bacteria from the blood stream, a secondary inflammation, but that primary forms exist is confirmed by their occurrence in patients without bacteremia and without demonstrable bacteria in the thrombus.

Acute Proliferative Arteritis Proliferation of cells in acute arteritis is observed almost solely in the intima. There are cases in which this is undoubtedly a proliferation of endothelial cells. In many, however, masses of swollen mononuclear cells with poorly staining cytoplasm, of uncertain origin, form masses piled up into the lumen of the artery. Thrombosis is not found except as a later manifestation and exudative cells are found not so noticeably in the intima as in the adventitia. Even in the latter situation, exudation may be scanty. Intimal proliferation is seen in many varieties of arteritis such as that observed in rheumatic fever, in syphilis and cases of more or less localized arteritis without known cause. It is reported



FIG. 5 Acute proliferative arteritis. Disease localized to region of gall-bladder and kidney. Female, aged 35 years. ($\times 190$)

by Wiese in pulmonary thrombo-arteritis, by Leriche and Froehlich in the arteritis following adrenal grafting, and by Kaunitz and by Yater and Cahill in ergotism. It may be found sometimes in periarteritis nodosa. It is reasonable to assume that as endothelial proliferation in glomerular capillaries signifies an inflammatory reaction, this lesion of arteries may be similarly interpreted. Proliferation of medial connective tissue cells, of fibroblastic type, as an indication of acute reaction is uncommon but may be found, especially in the florid stages of rheumatic fever.

Organizing Arteritis This is observed as a later stage of arteritis, particularly that which has been associated with thrombosis. The character

of the granulation tissue is not different from that observed elsewhere, except that as organization proceeds it is likely to be accompanied by canalization. Buerger considers the later vascular lesions of thromboangitis obliterans to be an organizing stage of a previous acute thrombo-arteritis.

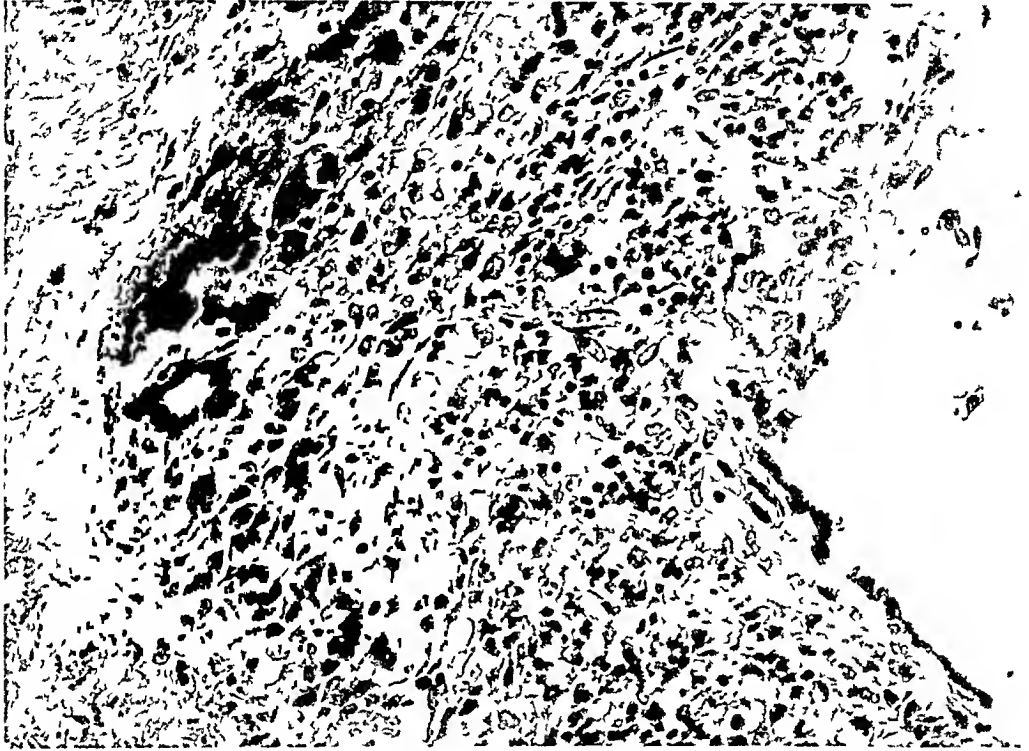


FIG 6 Organizing acute arteritis. Epicardial artery of a case of periarthritis nodosa. Female, aged 26 years. ($\times 300$)

Wiese describes it in primary pulmonary thrombo-arteritis. It is well seen in periarthritis nodosa and in other diseases where survival permits of organization.

Chronic Arteritis In this category are included progressive fibrotic disease of arteries, which do not show the lipoidosis, atheroma or calcification of arteriosclerosis. This differentiation cannot be considered inflexible because any dense fibrous mass may finally become fatty and calcified. That it is progressive, as required by definition of chronic inflammation, is assumed by the variation in the appearance in different arteries from the same patient. Only occasionally does it show lymphocytic infiltration. It differs from endarteritis obliterans, intimal arteriosclerosis and the senile medial disease of Monckeberg in that it involves two or more coats and when it occurs in the media is irregularly distributed and does not show calcification. It is particularly well illustrated in rheumatic fever, where the chronic arterial lesion resembles the chronic endocarditis. It occurs in

thromboangitis obliterans It is seen in the smaller arteries, such as the vasa vasorum in syphilis That this form of syphilitic disease is due to the direct action of spirochetes is doubtful, because they are not demonstrable in the lesion

On the basis of a single preparation it is often impossible to distinguish chronic arterial inflammation from involutional changes such as are observed in the senile uterus, ovary and other situations The same may be true of destructive and reparative phenomena in such lesions as chronic cholecystitis These difficulties are ameliorated if specimens from many parts of the body be available for study

DISCUSSION

The material upon which this classification is based was from patients who presented a wide variety of clinical manifestations Extensive acute arteritis may express itself with fever, leukocytosis, purpura and similar general phenomena If localized, as for example in the gall-bladder, kidney or appendix, etc (Plaut), the clinical features disclose the localization and general signs depend upon the severity of the disease As with arteriosclerosis of medium sized and small arteries, the immediate effects of acute arterial inflammations are referable to the effects within the parts diseased, but acute arteritis differs in that it presents more or less marked signs and symptoms of a general disease In one case of acute proliferative arteritis of kidney and perirenal structures, surgical removal of the diseased tissues resulted in apparently complete recovery as long as the patient could be traced (four years) In contrast, a case of chorea in a child resulted in death in a few weeks with widespread acute exudative arteritis, of rheumatic character Chronic arteritis is without accompanying clinical signs unless it be of sufficient degree to produce local atrophy and fibrosis with resultant physiological change, as is also true of arteriosclerosis These statements are in accord with the distribution and character of the lesions as outlined in the introductory paragraphs

The acute lesions described rarely occur as pure forms The combination of necrosis and exudation is worthy of special comment because this is the lesion seen most often in periarteritis nodosa In the typical cases the cells of the exudate include eosinophiles, both polymorphonuclear and mononuclear Aikin did not consider the eosinophile as an essential feature Middleton and McCarter mention eosinophilia of the circulating blood but do not emphasize eosinophiles in the exudate There is no mention of these cells in the reports of Bennett and Levine, of Yardumian and Cohen, or of Krahulik, Rosenthal and Loughlin Friedberg and Gross note the eosinophiles in one of their four cases and Curtis and Coffey, Bernstein and also Dungal in each of their cases Gruber, who suggested discontinuous hyperergic phenomena as the cause of the disease, paid little or no attention to eosinophiles, whereas Kline and Young suggest that the local eosinophilia

supports the hypothesis of allergic causes. Certainly a necrotizing-exudative arteritis occurs both in man and experimental animals without the general manifestations of periarteritis nodosa. While it would perhaps be too stringent to insist upon the finding of eosinophiles to establish the diagnosis, the local eosinophilia should be given a place of great importance. As emphasized by Klemperer, there are other features of significance if the original meaning of the term periarteritis nodosa is to be preserved, as for example, the presence of nodules visible to the naked eye or through the hand lens as well as the microscopic demonstration of aneurysms. With the criteria suggested, it should be possible to avoid the conclusion that a wide variety of acute arterial inflammations belong in the category of periarteritis nodosa.

Syphilitic disease of smaller arteries, especially those of the meninges, is characteristically exudative and necrotizing. Because spirochetes have not been found in the lesion (Spielmeyer), it has been thought to be due to "toxins." In a recent case observed in this department, spirochetes were found in abundance. Thus, this form of syphilitic arterial disease belongs in the proposed category of secondary arteritis, as is true of tuberculous arteritis and other forms, as for example that seen in typhus fever, hog cholera, brucellosis, etc.

In human material, involvement in variable degree of all the coats of the artery is usually found, although often the lesion is especially conspicuous in one or another of these layers. Thus it might be assumed that the inflammation begins in the entire wall as a unit. That this assumption is probably not valid is indicated by the experiments of Ramsey and her co-workers, who found that chemical, particulate or bacterial injury of the intima is first reflected in reaction in the perivascular tissues (adventitia and surrounding connective tissue) or the outer portions of the media. Exudation then extends through the media, appears to be temporarily hindered by the internal elastic lamina, but soon involves the entire wall. Thus it would be unwise to suppose that because a section of artery shows a given lesion to be especially prominent in one coat, that coat is the one primarily affected. The course and sequences of arteritis deserve extensive and detailed study.

SUMMARY

In addition to those inflammations of arteries of small and medium size due to extension of local inflammation or direct invasion of bacteria and other organisms, which may be designated as secondary arteritis, there are forms of arteritis due to unknown or ill-defined causes which can appropriately be named primary arteritis. The lesions found in these primary forms have been classified and include both acute and chronic varieties, the former varying from degenerative and necrotizing to exudative, proliferative and organizing forms. The chronic forms differ from arteriosclerosis in distribution of fibrosis in the three coats of the arteries and by delayed or ab-

sent secondary changes in the fibrous tissue. It is suggested that an improved nomenclature for the varieties of arteritis will aid in correlating descriptive morphological and clinical data so that a precise understanding of these diseases will be attained.

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HEALED BACTERIAL ENDOCARDITIS

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If we base our views about the course of subacute bacterial endocarditis solely upon routine observations made in the clinic, we must conclude that it is an exceptionally malignant disease, for almost invariably it ends in death. Reckoned from the time symptoms first appear the average duration of the illness is about six months and only seldom does the affected patient live longer than a year. In 1924 Thayer reported that of 206 cases, collected from the records of the Johns Hopkins Hospital, none had recovered. As far as I know the uniform mortality of the disease at that hospital has not changed during the past 12 years, for I am convinced that had a recovery occurred, this exceptional event would have been loudly proclaimed, and could not have escaped my notice. Certain I am, that no well-established instance of subacute bacterial endocarditis, which has been under my observation, has ever recovered. This depressing experience is by no means unusual, for many seasoned practitioners tell me that their results have been precisely the same. I think it is true that when the diagnosis of endocarditis lenta is securely made then most physicians regard the outcome as hopeless.

Nevertheless, in spite of this almost universal pessimism, it cannot be doubted that occasionally recovery does occur. However, not so frequently as is reported in the literature, for a careful examination of these reports reveals that in many the diagnosis has not been conclusively established. In some the blood cultures have been sterile, in others the evidence of an endocardial lesion is unconvincing, in still others the facts are so incompletely reported that it is impossible to identify the true nature of the illness. Many competent observers in discussions and under other circumstances merely state that in their experience so many patients have recovered without giving any clinical details. Knowing the established reputation of these physicians one cannot doubt the accuracy of their statements even in the absence of supporting facts. However, leaving all these reports aside, we may still find detailed and convincing accounts of many cures. I do not pretend to name them all but choose as illustrations those instances reported by Murray, Hemsted, Capps, Bogendorfer, Schottmuller, Perry, Kissing, and Kraiss.

I have omitted from this list the name of Libman because his reports contrast so violently with general experience that they must be noticed separately. Libman reports at least 3 per cent of recoveries in the usual

* Presented at the St. Louis meeting of the American College of Physicians, April 20, 1937.

type of the disease and is convinced that many more recoveries occur in mild cases which are often overlooked. He publishes brief notes of 17 recovered cases, some dying in a second or even third attack after intervals of many years. I must admit that Libman's results are more in accord with evidence obtained post mortem than are the usual results of other physicians. This is strong corroboration of the truth of his observations, if, indeed, any corroboration is needed for the observations of so distinguished a student in this field. Therefore it is interesting to ask what may be the reason for the divergence of these results.

The characteristic clinical symptoms of subacute bacterial endocarditis are fever, anemia, evidence of a valvular defect or a congenital abnormality, splenic enlargement and embolic phenomena. When these symptoms are well developed the diagnosis is assured. However, very often one or more of the symptoms is absent and then the diagnosis may be difficult. For instance, when there are no embolic phenomena, the disease, in its mild forms, may very closely resemble rheumatic fever. Indeed, often it is impossible to distinguish confidently between them. It is unnecessary to remind you how very difficult it is at times, even in the presence of loud murmurs, to be sure that there is an endocardial lesion, and yet without this confidence one can only surmise, but never state, that the patient has bacterial endocarditis.

The diagnosis of bacterial endocarditis can be made without actually demonstrating the presence of bacteria in the blood stream although this demonstration is always desirable and under circumstances, when the complete clinical picture is not developed, it is essential. However, it must be emphasized again and again that the mere presence of bacteria in the blood stream, when other characteristic symptoms, especially the undoubted presence of an endocardial lesion, are absent, does not warrant the diagnosis of subacute bacterial endocarditis. On many occasions pyogenic organisms gain access to the circulating blood but do not settle within the heart and the presence, say, of staphylococci in blood cultures and of a systolic murmur over the heart does not justify the diagnosis of bacterial endocarditis, especially not, if the observer reports that an examination made months later, when the patient had recovered, demonstrated the heart to be normal. It is now common knowledge that the *Streptococcus viridans*, the organism most often concerned in subacute bacterial endocarditis, frequently invades the blood stream when there is infection in the upper respiratory tract and no doubt less frequently with infections located elsewhere. Therefore, the presence of bacteria in the blood during the course of a febrile reaction does not signify that the endocardium has become infected, unless at the same time there is undisputed evidence of a valvular lesion or a congenital defect, and other characteristic symptoms of bacterial endocarditis are present.

Whether the remarkable groups of cases reported by Oille, Graham and Detweiler, of Toronto, and by Salus, of Prague, are real instances of

Streptococcus viridans endocarditis or instances of bacteremia without endocarditis is difficult to decide. Certainly, their experience is unique, and I can only say for myself, that to me the evidence upon which is based the diagnosis of endocarditis is unconvincing. Oille, Graham and Detweiler report an epidemic of 23 cases, mostly in children, observed during a period of six months. The constitutional symptoms were mild, fever slight or absent, there were no embolic phenomena, all recovered. The evidence of endocardial involvement consisted almost entirely of apical and aortic systolic murmurs. Only three showed slight enlargement of the heart. Blood cultures in all were positive for *Streptococcus viridans* but only one culture was taken in 17 of the cases. These results contrast with the report of Warren and Herrick who collected from the records of the Roosevelt Hospital 134 cases with positive blood cultures. In 40 the infecting organism was the *Streptococcus viridans*. Twenty-five of the 40 had endocarditis, of these 22 had died, three were still living but unimproved. Of the remaining 15 cases, without endocarditis, 10 had recovered.

It is reasonable to assume that instances of bacterial endocarditis with very mild clinical symptoms are the ones which have the best chance of recovery. Moreover, this assumption is strongly supported by postmortem observations. However, it is these mild cases which are particularly difficult to recognize. Often there is but little fever, anemia, though always present, may be slight, and appreciable splenic enlargement and embolic phenomena may be absent. Usually they are regarded as instances of rheumatic or syphilitic heart disease and the autopsy revelation, demonstrating bacterial endocarditis, comes as a great surprise. With experience, the diagnosis of bacterial endocarditis may often be proposed under these circumstances, but cannot definitely be made, unless cultures demonstrate repeatedly the presence of bacteria in the blood. Unfortunately, in these mild cases, only a small number of bacteria may be washed into the blood stream and undoubtedly, sometimes, they are present there only intermittently. Therefore, to recover them cultures must be made repeatedly and with great care. I cannot say to what degree technical skill in bacteriology may improve the diagnosis of these mild cases. As regards the gonococcus I am sure that success in cultivating it from the blood stream depends in large measure upon the experience and skill of the investigator. The gonococcus is often the infective agent in these mild cases of bacterial endocarditis and yet, although it is usually recovered from fulminating cases of the disease, it is very seldom demonstrated in the mild cases. Nevertheless, the conditions found at autopsy indicate plainly that during life many bacteria must have been discharged into the blood stream. As regards the *Streptococcus viridans* there is not the same difficulty in growing it. The methods are now standardized and with reasonable care should give uniform results. However, it is always possible that extraordinary care may be more often successful. It is a matter worthy of consideration.

Let it be understood that nothing is further from my intention than to explain, as due alone to imperfect or faulty technic, the well-known fact that it is usually difficult and often impossible to grow bacteria from the blood of patients with mild and protracted symptoms of bacterial endocarditis, even when the conditions found at autopsy demonstrate clearly that large numbers of bacteria, constantly or intermittently, must have escaped into the blood stream. As I have already remarked it is usually a very simple matter to recover bacteria from the blood of patients acutely ill. The difficulty arises only when the disease is mild and of long duration. This difference, I think, must depend chiefly upon the gradual development of immunological forces. When, with the passage of time, the body acquires a powerful system of defense, then, although bacteria are swept into the blood stream, they are immediately attacked and soon destroyed. There is abundant evidence of the efficiency of this mechanism. The very fact that suppuration so seldom occurs is difficult to explain upon any other assumption. Even when the infective agent is the *Staphylococcus aureus*, widely spread abscesses are seldom seen in subacute cases. Occasionally we are successful in growing organisms from the blood drawn by puncture from the brachial artery, whereas, repeated efforts to grow them from venous blood are unrewarded. Here we may suggest that many bacteria are removed from the blood during its passage through the capillaries, but it seems to me even more likely that the fact is due to the greater length of time allowed the forces of immunity to play upon the bacteria. The apparent contradiction that in the face of these destructive forces bacteria still grow freely upon the infected valves is explained simply by the location of the bacteria, a location which shields them safely from harm. If you will look upon the stained section of an infected valve you shall see that the bacteria are accumulated beneath the margin of the valve where no blood vessels penetrate, and where they are secure from the reach of injurious chemical substances in the blood which bathes the valve, and from attack by leukocytes which may settle upon its surface. From this sheltered home colonies wander out towards the base of the valve but they do not penetrate far, for when they reach the area supplied by blood vessels they quickly perish.

I can propose only three possible explanations for the unusual results which Libman reports. First, being especially interested and experienced in the diagnosis of bacterial endocarditis he recognizes many mild cases which would escape the notice of average observers. Second, he is more indefatigable in the search for bacteria in the blood stream. Third, his technical resources in bacteriology are superior to those of the average laboratory.

When now we turn from the clinical experience with bacterial endocarditis and regard the disease from the standpoint of the pathologist we shall see prognosis in a different light. I think the pathologist, entirely unacquainted with the clinical course of the disease, and basing his opinion

solely upon what he observes at the postmortem table, would be surprised to hear that very few patients recover. In all but the very acute cases he is accustomed to find unmistakable evidence of healing. In one case, although there are active vegetations along the margins of a valve, in other portions dense fibrosis and calcification show where previously active lesions have healed. In another case, the process is mildly active upon one valve, whereas, another valve is scarred and contracted showing no longer vegetations or bacteria. In still another case, there is scarring and calcification of one or more valves without the slightest remaining evidence of infection, only the scarred remnants of infection long past. In a word, he sees almost regularly a strong tendency to healing, not infrequently a state of affairs where healing has become nearly complete so that he remarks, "if the patient had lived a little longer surely he would have recovered", and occasionally only stiff fibrotic valves as evidence that a previous lesion has completely healed.

The object of this communication is to attempt to bring our clinical and pathological experience more nearly into accord. This has been done before, for instance, by Libman and by Weiss and Rhoads. Still I think the subject is worthy of repeated attention. Those who are accustomed to follow patients from the ward to the postmortem room soon become convinced that in the clinic they fail to recognize many cases of bacterial endocarditis, and, from the character of the lesions there observed, that many patients recover and then live on for years with the usual evidence of a valvular defect. To illustrate these facts I have selected a few recent observations.

CASE I

L. B., 29 years, female, colored, single

A colored housemaid, then 27 years of age, came to the Gynecological Clinic of the Out-Patient Department of the Johns Hopkins Hospital on February 9, 1932, complaining of pain in the abdomen and too frequent menstruation. The diagnosis was made of right-sided, chronic inflammatory pelvic disease and myomatous uterus. She returned to the Medical Clinic of the Out-Patient Department on January 30, 1933, complaining of palpitation of the heart and shortness of breath. Two days later she was admitted to the hospital. There she stated that she always had been well, except for the menstrual disorders for which she had gone to the Gynecological Clinic, until December 27, 1932, when she was taken during the night with severe pain about the umbilicus. Later she had pain on the left side of the chest which persisted for three days and then disappeared. This pain was severe and was increased by deep breathing. During the attack the patient had nausea and vomited on several occasions. When these symptoms came on the patient had had for some days a slight cold. After the attack of pain she had cough, with a little expectoration, which at times was spotted with blood. She was quite sure that she had had fever. After the attack she was up and about for a few days but she then began to notice that she was very short of breath and that the heart beat rapidly and forcefully on slight exertion. The shortness of breath grew steadily worse and soon she was unable to lie down in bed. After 10 days her symptoms improved somewhat and she tried to work, but immediately became so short of breath that she had to give it up. She then noticed that her ankles were swelling and that palpitation and weakness were growing more pronounced.

Examination Temperature, 100.2°, pulse, 102, respirations, 48, blood pressure, systolic 90, diastolic 60

The patient was a well-developed, poorly nourished colored woman, propped up in bed, breathing rapidly but not in great distress. There was no cyanosis and no edema other than a little pitting over the shins. She evidently had lost weight. The mucous membranes were rather pale. The eyes were normally prominent, extra-ocular movements well performed. Pupils were equal, reacted actively to light. The fundi showed no abnormality. The teeth were in poor condition with marked pyorrhea. The pharynx was slightly injected, the tonsils were enlarged and scarred. Glands at the angles of the jaw were somewhat enlarged. Otherwise there was no glandular enlargement. The thyroid was just palpable. Trachea was in the midline.



FIG 1 Heart of Case 1 For description see text

The chest was well formed and symmetrical. The lungs showed no abnormality other than a few moist râles at the right base. The heart was greatly enlarged. There was a diffuse forcible impulse all over the precordium. The apex beat was in the fifth interspace, 11 cm from the midline. At the apex the shock of the first sound could be felt and at the base the shock of the second pulmonary sound. At the apex there was also a presystolic thrill. The area of cardiac dullness measured 5½ cm to the right, and 12 cm to the left of the midline. At the apex the first sound was loud and booming in quality, it was immediately preceded by a short rumbling presystolic murmur, and was accompanied and followed by a loud, harsh systolic murmur, widely transmitted. It was well heard in the axilla and below the angle of the scapula in

back The second pulmonary sound was greatly accentuated Rhythm was irregular due to the occurrence of very numerous extrasystoles The pulse was soft, rapid and of small size The vessel walls were not thickened The abdomen was normal in appearance, the walls were soft and relaxed, no tenderness, no masses were felt The edge of the liver was 3 cm below the costal margin, it was slightly tender The spleen was not enlarged The pelvic examination revealed a myomatous uterus The rectal examination was negative The neurological examination was negative

Course in the Hospital After a period of rest with digitalis, the patient rapidly improved and at the end of six weeks was up and about the ward in comfort

Laboratory Examinations

Blood Count 2/1/33 Hgb 54 per cent, R B C 3,550,000, W B C 8,900
3/18/33 Hgb 72 per cent, R B C 4,700,000, W B C 9,600

Wassermann reaction was strongly positive

Blood Culture 2/10/33 No growth

Lumbar Puncture 3/7/33 10 cc clear, colorless fluid withdrawn No evidence of increased pressure No cells Pandy negative Wassermann reaction negative Colloidal mastic test negative

Urine Specific gravity varied from 1.014 to 1.030 Occasionally there was a trace of albumin but usually none The sediment contained a few pus and epithelial cells

The temperature on admission varied from 99° to 100.4° On February 23 it rose to 102° following the extraction of an infected tooth Subsequently it fell again, ranging between 98.6° and 100°

The pulse rate varied from 70 to 110

Roentgenogram 2/2/33 Tele M R 68, M L 103, A 45, T 273

The heart is very much enlarged Changes in the lungs are secondary to the cardiac condition

Electrocardiogram 2/7/33 Normal sinus rhythm T₂ inverted There is a shift of 21 degrees of the electrical axis on change of position

Course after Leaving Hospital The patient left the hospital on March 18, 1933 and was referred to the Syphilis Clinic for treatment She reported there on March 23 and received an injection of bismuth She was comfortable for only about one week after discharge when the shortness of breath returned Apparently this was inaugurated by a cold She was hoarse and had cough with mucopurulent expectoration After this the shortness of breath grew worse and edema again appeared She entered the hospital the second time on March 21, 1933

Examination Temperature, 100°, pulse, 90, respirations, 26, blood pressure, systolic 90, diastolic 62

Examination on this occasion showed essentially the same conditions reported on the first admission Dyspnea was not intense, she could lie flat without becoming short of breath There was no cyanosis The edema was somewhat more marked than on the first admission, there was pitting over the tibiae and over the sacrum The liver also was more markedly enlarged, extending to the level of the umbilicus On this occasion the pulse at times was regular, at other times there were numerous extrasystoles, and on still other occasions, for brief periods, there were paroxysms of fibrillation

Course in the Hospital (Second Admission) The patient was given digitalis She became nauseated and vomited frequently Later theocin was given This seemed also to bring on nausea Although on admission the patient's condition was far from desperate, she grew progressively worse The heart seemed gradually to enlarge, certainly it was larger than during the first admission Numerous râles were heard over the lower lobes of both lungs and signs soon developed suggesting a small pleural effusion on the right Breathing became more and more difficult

The peripheral veins were greatly engorged and the patient became cyanosed. On April 7, 1933, eight days after her second admission to the hospital, she suddenly died.

Laboratory Examinations

Blood Count 3/31/33 Hgb 62 per cent, R B C 3,200,000, W B C 15,800

Urine Specific gravity varied from 1.020 to 1.030. There was a trace of albumin.

A small number of pus cells and a few R B C in the sediment.

Electrocardiogram 4/6/33 Normal sinus rhythm P-R interval 0.22 sec

P-waves broad and notched in all leads T₁ inverted Sinus tachycardia

The temperature ranged from 99° to 101°

The pulse rate ranged from 80 to 120

The clinical diagnosis made upon the hospital ward was rheumatic heart disease, mitral stenosis and insufficiency. However, a number of observers suggested the possibility of bacterial endocarditis and when, after death, the case was finally discussed at the clinical-pathological conference, the diagnosis of bacterial endocarditis was preferred. That this diagnosis was not seriously considered during life is demonstrated by the fact that only one blood culture was taken. In addition to the clear evidence of a mitral valve lesion, anemia and a low-grade fever were conspicuous elements of the clinical features of the disease. This made it certain that the patient must have had either an active rheumatic infection or bacterial endocarditis. The rapid course of the disease was the peculiar feature which led finally to the acceptance of the diagnosis of bacterial endocarditis. From the very first onset of symptoms, on December 27, 1932, to the date of death, April 7, 1933, was a period of only a little over three months, and although improvement occurred while the patient was in the hospital, carefully treated and solicitously shielded, still, the improvement was very superficial, for only one week after leaving the hospital severe symptoms returned and shortly thereafter she died. What a contrast this is to the usual course of rheumatic heart disease. Very seldom does the rheumatic patient fail to improve satisfactorily during the first attack of heart failure and usually, long periods of relative comfort separate recurring attacks.

The postmortem examination revealed the characteristic lesions of bacterial endocarditis. The striking feature of the lesions was the advanced healing which had taken place. The valves were thickened and fibrous, in places calcified, the vegetations consisted mostly of hyaline masses and some were undergoing rapid organization. Here and there on the surface were crops of bacteria. These were gram-negative cocci, in all probability gonococci, although they did not grow in cultures and therefore could not positively be identified. There was no evidence of active or preexisting rheumatic disease. The valvular infection seemed to be a primary one, due to the gonococcus.

Brief notes from the autopsy report are as follows:

Anatomical Diagnosis Subacute bacterial endocarditis involving the mitral valve (gram-negative cocci) transplanted on intraventricular septum. Hyaline vegetations on auricular endocardium, hypertrophy of left ventricle of the heart, chronic

passive congestion of lungs and liver, infarction in spleen, thrombosis of pelvic veins, pulmonary emboli, fresh pulmonary infarcts, pulmonary edema and lobular pneumonia, myomatous uterus, chronic bilateral salpingitis, intraperitoneal adhesions

Dr. F. B. Kindell's note on the heart: The heart is enlarged, weighing 480 grams. The surface of the right auricle shows areas covered by tough little granules of organized exudate. There are punctated hemorrhages beneath the epicardium of the right ventricle. The right ventricle is a little hypertrophied. The tricuspid and pulmonary valves are thin and delicate. The left auricle is moderately dilated. There is a roughened patch in the auricular endocardium some distance above the mitral valve. Some of these thickenings are old and smoothly covered by endocardium, other little patches are made up of tiny granules which are tough and some are suggestively gritty. The mitral valve is thickened. The margins of the leaflets are gray and fibrous. The change is most marked along the edge of the aortic leaflet. There are also fresher greenish-gray vegetations along the line of closure but they are most pronounced along the chordae tendineae which are attached to one wing of the aortic leaflet. Most of these are broken. The larger masses of vegetations are distinctly tough, apparently partly organized. The marginal fringes are softer and crumbly. Three centimeters below the aortic orifice there is a granular patch suggesting partly healed vegetations on the endocardium of the interventricular septum. This is precisely in the position where the flapping loose ends of the chordae tendineae must have brushed the ventricular wall. The aortic cusps showed no lesions. The aorta, except for fine streaks of fat, has a normal intima. The larger branches of the coronary arteries are normal.

Microscopical Report: The mitral valve is quite thick and fibrous. In the small section which shows the fresher vegetations it is found that these also are of some duration. The center of the mass is calcified and it is only on the surface that crops of bacteria are found. These are gram-negative cocci, somewhat smaller than gonococci generally are. The lesion from the interventricular septum shows a thickened endocardial layer with rather numerous scattered mononuclear cells. The vegetations on the surface are hyaline. The lesions from the lining of the auricle are quite fibrous but there are hyaline masses on the surface. There are only a few minute scars in the myocardium and on the whole there is little support for the view that the older thickening of the mitral valve and the hyaline lesions in the auricle were originally rheumatic.

CASE II

J. C., 51 years, male, colored, married

A colored laborer, then 48 years of age, came to the Medical Clinic of the Out-Patient Department of the Johns Hopkins Hospital December 15, 1933, complaining of pain in the lower part of the abdomen and shortness of breath. At 19 years of age he had had an attack of rheumatic fever lasting three months. This had come on after exposure. All of the joints had been involved and were swollen and inflamed. Ten years before admission he had had an attack of sciatica in the left leg and following this he had had six or eight recurrent attacks. He said he never had had either gonorrhea or syphilis, although he described symptoms that made it almost certain that he had had a gonococcus infection at 18 years of age. In other respects he had been a healthy man, working hard until three weeks before coming to the Out-Patient Department. At that time he had had pain in the lower part of the abdomen soon followed by shortness of breath. The pain in the abdomen was described as a dull soreness. The shortness of breath progressively had gotten worse and for some nights before coming to the hospital he had been unable to lie down.

Examination: Temperature, 98°, pulse, 96, respirations, 20, blood pressure, systolic 160, diastolic 80, weight, 151 lbs.

The patient was a well-nourished colored man in no distress. The pupils reacted

actively. The teeth were in bad condition. There were no enlarged lymph nodes. The thyroid was not enlarged. The lungs were clear except for a few rales at the bases. The heart was enlarged especially to the left. At the apex there was a blowing systolic murmur transmitted to the axillary area. In the aortic area there was a harsh, rough systolic murmur transmitted into the vessels of the neck. There was a systolic thrill felt over the base. There was a blowing diastolic murmur down the left border of the sternum. There was marked peripheral pulsation and the pulse had a decided collapsing quality. The peripheral vessels were tortuous and thickened. The abdomen was somewhat distended and there was thought to be free fluid in the peritoneal cavity. The edge of the liver was felt three fingers-breadth below the costal margin. The spleen was not felt. The reflexes were all normally active.

The specific gravity of the urine was 1.024. There was a trace of sugar, no albumin. The Wassermann reaction on the blood serum was negative.

Roentgenogram. Fluoroscopic Examination. Heart enlarged, aorta diffusely dilated and rotated, no evidence of aneurysm. Some increase in the peribronchial markings. Marked infiltration at the bases probably secondary to the cardiac condition.

Film. Cardiac shadow enlarged, aorta dilated. Secondary changes in both lungs.

The patient returned to the Out-Patient Department September 4, 1936. On that occasion the Wassermann reaction was found to be positive. He then was quite short of breath and there was edema of the legs. A roentgenogram is reported. Cardiac shadow enlarged, aorta dilated, secondary changes in both lungs. Interlobar thickened pleura, right side.

The patient was admitted to the hospital September 22, 1936. There he stated that following his visit to the Out-Patient Department in December 1933 he had been quite comfortable until six weeks before this admission. Then shortness of breath on exertion had developed and gradually had increased so that he had been unable to lie down in bed and had had to spend the nights sitting in a chair. His ankles had been swollen for a month.

Examination. Temperature, 99.5°, pulse, 96, respirations, 28, blood pressure, systolic 115, diastolic 50.

The patient was described as a short, squat, pudgy-looking, middle-aged Negro. He was propped up in bed with only moderate respiratory distress. The veins in the neck were engorged. The pupils were equal and active. There were no enlarged lymph nodes. The thyroid was not enlarged. There were coarse rales at the bases of both lungs. On the right below the angle of the scapula the percussion note was a little impaired and the breath sounds were somewhat diminished in intensity. There was violent pulsation over the heart. The apex beat was a forcible thrust in the seventh interspace at the anterior axillary line. At the apex both a systolic and a diastolic murmur were heard, the latter becoming louder toward the base. The diastolic murmur was particularly loud to the left of the sternum. No thrill could be felt. The right pulse was somewhat fuller than the left. The blood pressure was the same on both sides. The abdomen was somewhat distended. The edge of the liver was felt three fingers-breadth below the costal margin. The genitalia showed no abnormality. The rectal examination was negative. The reflexes were obtained but were somewhat hypoaactive.

Course in the Hospital. On admission the temperature was somewhat elevated and during the following four days it varied between 101° and 103°, then for three days it fell almost to normal but soon rose again varying at first between 99° and 102°, later between 101° and 104°. There was a moderate degree of anemia. From time to time there were severe attacks of dyspnea. At other times he was delirious. A friction rub developed over the right lower lobe and the roentgenogram showed evi-

dence of consolidation, it is stated in the report, of the right upper lobe. Later there were dullness and fine râles over the upper portion of the left chest and a roentgenogram showed spreading consolidation on the left side. There was very little cough and almost no expectoration. Still later, signs suggesting fluid in the right pleural cavity developed. On October 10 the right pleural cavity was tapped and 30 c c of bloody fluid were removed, which contained 12,500 leukocytes per cu mm. Most of



FIG 2 Heart of Case 2 For description see text

the cells were polymorphonuclears containing gram-positive diplococci. There were also chains of diplococci, thought to be pneumococci, in the fluid. Cultures yielded a heavy growth of *Alphia streptococci*. As these signs in the lungs were developing the temperature and pulse rate rose to a higher level, the patient became more and more irrational and exhausted, and while desperately ill he died suddenly on October 10, 1933.

Laboratory Examinations

Blood Count Hgb 58 per cent, R B C 4,570,000, W B C 6,920

Later the leukocyte count rose and varied from about 10,000 to 20,000

Blood Culture No growth

Urine Specific gravity 1.023 No sugar A large amount of albumin on admission, later none Many leukocytes and a few casts in the sediment

Roentgenograms

- 9/26/36 Chest General haziness of lung field probably due to movement of patient Area of consolidation of right upper lobe, probably lobar pneumonia
- 10/2/36 Chest There is now clouding in the left mid-lung field compatible with pneumonia
- 10/8/36 Chest Heart and aorta apparently enlarged Diffuse clouding in right lung especially in mid-portion, probably pneumonia
- 10/9/36 Chest There is only a small amount of fluid in the right chest, the majority of the changes are due to a pneumonic process
- Electrocardiogram Fairly deep S-waves in Leads I and II T_1 upright and small Low take-off of S-T segment in Lead II, ending in a biphasic T-wave T_1 inverted Changes in Leads I and II compatible with those seen following pulmonary embolus T-wave changes probably are due to digitalis

From these clinical data I do not see how it would be possible to make any diagnosis of the heart condition other than syphilitic aortitis with aortic insufficiency The patient had been examined three years before the onset of his final illness and at that time showed the characteristic signs of aortic insufficiency He had had mild symptoms of myocardial failure but no fever, no embolic phenomena and no splenic enlargement The Wassermann reaction had been positive Then followed a period of nearly three years without symptoms, at the end of which shortness of breath and swelling of the ankles again came on During his second admission to the hospital the illness was dominated by the symptoms of a severe pulmonary infection which was correctly diagnosed as an infected pulmonary infarct The symptoms of myocardial failure were inconspicuous

Autopsy revealed the characteristic lesions of bacterial endocarditis which had almost completely healed In stained sections the infecting organism was a gram-positive coccus, in all probability the *Streptococcus viridans* There was no evidence whatsoever of a past or present rheumatic infection or of syphilitic aortitis It may be that the aortic valves were congenitally bicuspid but, on account of the great deformity of the valves caused by the infection, this point could not be definitely settled

When we consider the clinical course of events, and view the conditions found at autopsy, we cannot resist the conviction that in this patient the bacterial endocarditis eventually would have healed, had he not died untimely of the pulmonary complication

Portions of the autopsy report are added

Anatomical Diagnosis Subacute bacterial endocarditis aortic valve, dilatation and scarring of sinuses of Valsalva (healed mycotic aneurysms, malformation?, ulceration), scarring of mitral valve, hypertrophy and dilatation left ventricle, scars, left ventricle, mural thrombi auricular appendage, emboli in pulmonary arteries, infarcts, infected gangrenous infarct, right lower lobe, infarcts in spleen, hemorrhages in kidneys, hemorrhagic pleural effusion, right, ascites, chronic passive congestion lungs and liver, small angioma of liver

Dr W C MacCallum's note on the heart The heart is quite large, the surface in general is smooth but there are pearly patches over the right ventricle and small

lenticular nodules along the coronary arteries. The coronaries are fairly straight. The left anterior descending branch shows some patches of sclerosis, these are very thin. The right is almost smooth throughout. The right auricle shows a smooth endocardium. There is a very small thrombosis in the tip of the auricular appendage. The tricuspid valve is in part quite delicate. A portion of it shows a thickening and rolling of the margin and shortening of the chordae tendineae.

The pulmonary valves are delicate. The left auricle seems hardly changed. The mitral valve is a little thickened along its line of closure and perhaps slightly contracted. The aortic leaflet of the mitral valve shows a curious translucency throughout most of its extent with a margin of more opaque white. There it is roughened a little by dark red flecks which are extremely small. There is no actual vegetation to be seen. At the beginning of the posterior leaflet there is very marked thickening which has been taken for section. This has a roughened and reddened surface and on section is about 4 mm thick, translucent and gray. It passes on into the chordae. Along the aortic segment particularly the chordae tendineae are thickened and apparently fused along the thickened margin of that valve. Along the edge of the other valve, that is the posterior segment, they are separated but there is a distinct thickening extending at least to the middle of the valve, of the margin and the line of closure.

The margin of the sinus of Valsalva at the root of the aorta is so completely altered that only a photograph or sketch can describe it. The aortic valves are practically fused together. There is only one point at which the ordinary approach of two valves to one another is seen and that is at the base of the mitral between half of the left segment and half of the posterior segment. The rest forms one thick, rigid band which is perforated by a large hole and by smaller holes, white and roughened and covered with vegetations but the sinuses are all run together as far as they lie behind this great shelf-like structure.

The orifice of the left coronary is wide, that of the right coronary is very wide but seems practically unchanged, although in the remaining space which extends deep down below these coronary orifices, there are great depressions lined by pearly scar-like material, in places covered by fresh vegetations, in places extending so as to isolate cord-like strands from the aorta down to the sinus.

Just above the level of the sinus of Valsalva the aorta becomes perfectly normal and smooth. This, however, extends only to about the middle of the arch. Below the aortic valve the septum membranaceum is thickened by gray or pearly bands. The back of the mitral valve is rigid, yellowish and roughened. Toward the aortic valve it is much more roughened, evidently from the implantation of a vegetation. The myocardium is not much affected.

The aorta past the margin of the large vessels shows some sclerotic change. Below that in the thoracic aorta the wall is fairly elastic. It is flecked with tiny patches of whitish opacity and there is a delicate striation along the whole course. These flecks become a little more emphasized below the renals and there are some yellow patches.

The left lung is smooth externally throughout the upper lobe. In the lower lobe there are two projecting patches which are somewhat reddened. On section the upper lobe seems air-containing except for a small patch which is fairly firm in the lower part. In the middle of the lower lobe there is a quite distinct infarct.

The right lung shows a fibrous, somewhat hemorrhagic exudate on the surface. The upper lobe shows a patch of consolidation in its lower margin which on section is somewhat hemorrhagic and shows a thrombus in the central blood vessels. It is quite sharply outlined. It has in general the appearance of an infarct. In the middle lobe the brown pigmentation of the lung is particularly striking but it seems to be air-containing throughout.

In the lower lobe there is a large area of consolidation which is deep red and has

in general something of the appearance of an infarct but the central part is hollowed out into ragged cavities with greenish, discolored walls which communicate with one another. The large vessel passing to this area is plugged by a thrombus.

Microscopical notes. Cultures from the valves showed many different organisms. In smears the predominant organism was a gram-positive coccus occurring in threads and in long and short chains.

CASE III

W. S., 50 years, male, colored, single.

A colored laborer, 50 years of age, entered the Johns Hopkins Hospital, January 24, 1934, complaining of shortness of breath. He had been in the hospital previously from January 16 to January 19, 1922. The diagnosis was syphilis, aortic insufficiency, chronic alcoholism. Following his discharge in January 1922, the patient



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FIG. 3 Heart of Case 4. For description see text.

apparently had gotten along well and had worked hard. When admitted to the hospital January 24, 1934, he said he had been somewhat short of breath for a great many years but this had caused him no great inconvenience until December 1933 when he had become progressively more and more short of breath and the ankles and legs had become swollen. At the end of December he had had some fever and from then on his shortness of breath had become very severe. He had been unable to lie flat in bed, indeed, had spent most of the time sitting in a chair.

Examination. Temperature, 99.6°, pulse, 100, respirations, 26, blood pressure, systolic 190, diastolic 60.

The patient was in great respiratory distress, it was difficult for him to talk on account of the shortness of breath, his respirations were rapid and labored. He had an anxious expression. He had a rasping cough and occasionally brought up a little mucoid sputum. Breathing was Cheyne-Stokes in character. There was marked edema of the legs and over the lower part of the back. He was very cyanotic. The eyes were normally prominent, pupils equal, regular, reacted actively to light and on accommodation. Extra-ocular movements were well performed. The retinal arteries were somewhat narrow and tortuous, and the veins rather full. The teeth were in very poor condition. The pharynx was somewhat injected. No enlarged superficial lymph nodes. Thyroid not enlarged. The chest was full and rounded, symmetrical. The lungs were clear except for numerous moist râles over the lower lobes. The heart seemed to be greatly enlarged. No localized apex beat could be made out. The area of cardiac dullness measured 4 cm to the right and 12 cm to the left of the midline. There was a band of dullness over the manubrium measuring 7 cm. The heart's action was very rapid but regular. At the apex a definite thrill could be felt, its time in the cardiac cycle could not be determined. The first sound at the apex was very loud and was preceded by a rumbling murmur, late in diastole, it was accompanied and followed by a soft, blowing systolic murmur. Over the body of the heart there was a proto-diastolic gallop. In the aortic area the sounds were heard with difficulty. There was a distant, rough systolic murmur, the second aortic sound was not clearly distinguished and seemed to be replaced by a diastolic murmur which was heard also to the left of the sternum. The second pulmonary sound was accentuated. The pulse was regular, moderately collapsing in quality, a capillary pulse was visible in the nails. There was moderate thickening of the peripheral vessels and considerable throbbing. The abdomen was prominent, there was a moderate degree of ascites. The liver was enlarged, extending a hands-breadth below the costal margin. The spleen was not felt. Genitalia showed nothing abnormal. The reflexes were normally active.

Course in the Hospital The patient made a prompt and remarkable recovery. After three or four days he was comfortable and at the end of five days was able to lie flat in bed. As the heart rate slowed the sounds could be more carefully observed. The apex beat now could be felt in the sixth interspace almost as far out as the anterior axillary line. All observers agreed that the first sound at the apex was loud and that there was a definite rumbling murmur late in diastole. There also was a systolic murmur and an early diastolic murmur. At times the diastolic murmur at the base was not very pronounced and some observers even doubted the existence of aortic insufficiency. However, in the end everyone agreed to the presence of aortic insufficiency and most observers were of the opinion that there was definite evidence of mitral disease as well. There seems to have been a remarkable reduction in the size of the heart as the patient improved, for a roentgenogram taken shortly before his discharge shows the heart to be but little enlarged. As the patient improved a very loud systolic murmur was heard in the tricuspid area. The blood pressure on admission was elevated, on one occasion as high as systolic 200, diastolic 90. As he improved the blood pressure gradually fell and when he was discharged from the hospital the reading was systolic 142, diastolic 58. On one occasion it had been as low as systolic 112, diastolic 56. He was discharged in good condition on February 27, 1934.

Laboratory Examinations

Blood Count	Hgb	R B C	W B C
On admission	74 per cent	3,700,000	12,750
On discharge	110 per cent		7,840
Wassermann reaction on the blood serum	Negative		
Blood Culture	No growth		

Urine Specific gravity 1.016 to 1.022 A trace of albumin No sugar A moderate number of leukocytes and a small number of casts in the sediment
Temperature on admission varied from 98° to 100° On discharge it was oscillating between 98.6° and 99.6°

Electrocardiogram Normal sinus rhythm Levogram Slight slurring of QRS complexes in all leads T-waves inverted in I and II, iso-electric in Lead III

Roentgenogram

Chest Cardiac shadow slightly enlarged Tuberculous, fibroid infiltration left upper and middle portion of lung

Tele M R 47, M L 98, A 62, T 28

After discharge from the hospital on February 27, 1934, the patient made a number of visits to the Out-Patient Department and then returned no more On October 22, 1936, he was admitted to the City Hospital desperately ill and died later on the same day He stated that during the two previous months he had suffered from ever increasing shortness of breath, swelling of the legs, and cough with frothy, blood-tinged sputum Only a hurried physical examination could be made, the notes of which record moderate enlargement of the heart, the signs of mitral stenosis and insufficiency, and the usual evidence of chronic passive congestion The signs of aortic insufficiency were overlooked or misinterpreted

Considering the clinical evidence presented by this patient one is forced to make the diagnosis of rheumatic heart disease He was first observed in 1922 at which time he had a characteristic aortic insufficiency without symptoms He remained well until 1933 when the first symptoms of myocardial failure came on Again, examination revealed the signs of aortic insufficiency and in addition the signs of a mitral lesion He died of heart failure in 1936, fourteen years after the valve lesion had first been discovered

I shall not dwell upon the erroneous diagnosis of mitral stenosis, for it is only too well known how difficult it is to decide upon the condition of the mitral valves in the presence of aortic insufficiency I wish merely to remark that the clinical assumption that in addition to aortic insufficiency the patient did have mitral stenosis, made the diagnosis of rheumatic heart disease seem doubly secure

As a perusal of the autopsy notes will show there was no disease of the mitral valves Only the aortic valves were affected and these in a manner which leaves little doubt that the original infection was bacterial and not rheumatic We must realize that it is never possible from the inspection of old healed scars to state with complete assurance the precise nature of the injury which caused them However, in this instance the appearance of the valves is so characteristic that a positive statement is justified even though not entirely certain

Anatomical Diagnosis Scarring, calcification, insufficiency and stenosis of the aortic valve (healed bacterial endocarditis?), calcified plaques above commissures of the aortic valve, history of treated syphilis, history of hypertension, cardiac hypertrophy and dilatation, scars in the myocardium and epicardium, chronic passive congestion, anasarca, calcified tubercle at apex of left lung and in left bronchial lymph node, slight emphysema and anthracosis, (long standing history of mitral stenosis)

Dr S S Blackman's note on the heart The heart is quite large The chambers are all dilated and hypertrophied but the hypertrophy is chiefly on the left side There are a few tendinous patches on the epicardial surface The tricuspid valve is practically normal At one point, there is slight thickening along the line of closure of one anterior leaf The left auricle shows no evidence of an old rheumatic patch The mitral valve is practically delicate and looks anatomically competent At the junction of the anterior and posterior cusps, there is a slight thickening along the line of closure in a small localized area The endocardium above is very finely granular The chordae tendineae are not scarred or shortened There are only a few small yellow patches in the aortic leaf of the mitral valve The aortic cusps are all very much thickened and deformed The thickening and calcification which are marked are most marked along the line of closure and the changes further down where the valves fuse with the endocardium of the septum are much less marked The commissures are all greatly thickened and not calcified There are calcified nodules projecting toward the ventricle and into the sinuses of Valsalva There is a good-sized, circumscribed plaque in the aorta at the point of insertion of each cusp These plaques are now calcified The largest one is above the point of insertion of the right and left cusps and this plaque is about 2 cm in diameter The adjacent margins of the right and left aortic cusps below this plaque are fused together to form a calcified mass which is nearly 1 cm wide It bulges out towards the ventricle for nearly an equal distance and where the separation finally does take place, there is a wide gap between the two in which there is a little coagulated blood and some yellowish granular material suggesting fibrin All of the altered commissures are pulled down and somewhat retracted and the valve is evidently insufficient and somewhat stenosed too The mouths of the coronaries are not narrowed and there is very little coronary sclerosis However, one can see definite gray scars in the myocardium near the base In the posterior papillary muscle there are numerous evident gray scars There is not enough evident sclerosis of the coronary arteries to account for these scars However, the mouth of the right coronary lies between the two plaques already described, and these do extend in the aorta as far as the very edge of the coronary mouth Although it is not narrowed, the elasticity of the aorta on either side of it is evidently lost The ascending aorta besides the plaques mentioned is perfectly delicate and smooth for in the rest of the aorta too, there is very little sclerosis There are a few calcified plaques in the arch and in the lower part a few yellow streaks and one or two little calcified plaques but no definite syphilitic lesions and really very little arteriosclerosis

The other organs show chronic passive congestion

CASE IV

G D, 65 years, female, white, divorced

A white woman, 65 years of age, entered the Johns Hopkins Hospital October 12, 1935, complaining of shortness of breath and swelling of the legs She always had been a hard-working woman and was well until four years before admission when she began to have attacks of indigestion The symptoms became so severe that she entered a hospital at Philadelphia where they treated her by washing out the kidneys After leaving the hospital she began to notice shortness of breath on exertion and occasionally the ankles were somewhat swollen The shortness of breath gradually increased and at the end of 1933 she was so troubled with dyspnea and swelling of the legs that she had to give up her work and go to live with a relative Even though she now lived very quietly she did not improve Her shortness of breath finally became so severe that she entered a hospital at Lebanon, Pa When she left the hospital at the end of five weeks she was much better

One year before her admission she had an upper respiratory infection and all

of her old symptoms returned. She was quite short of breath and her legs were swollen. From then on she was always short of breath and the ankles were swollen from time to time. Five weeks before entering the hospital the abdomen began to swell and her shortness of breath became more and more severe. Three days before admission she had nausea and severe vomiting. She came to Baltimore and was admitted to the hospital through the Accident Room.

Examination Temperature, 98.4°, pulse, 145, respirations, 28, blood pressure, systolic 166, diastolic 110.

The patient was a well-developed, well-nourished woman propped up in bed with a moderate degree of respiratory distress. She was very deaf which made it difficult to get a detailed history. There was a little cyanosis of the lips and nails. There was extensive edema of the legs, ankles, thighs, over the sacrum and back and a little over the arms and wrists. The eyes were normally prominent, pupils were equal, reacted actively. There was a slight arcus senilis. The retinal veins were somewhat engorged, the arteries somewhat narrowed and tortuous though not conspicuously so. There was slight compression of the veins where the arteries passed over them. A few small recent hemorrhages were seen. All the teeth had been extracted. The pharynx showed nothing remarkable. There was no enlargement of the superficial lymph nodes. Thyroid was not enlarged. The chest was well formed, it moved somewhat as a whole. The lungs were clear except for a few moist râles over the lower front on both sides and in back below the angle of the scapula. The apex beat of the heart was in the fifth interspace 9 cm. to the left of the midline. Area of cardiac dullness measured 5 cm. to the right and 11½ cm. to the left of the midline. The heart's rhythm was totally irregular. The first sound at the apex was followed by a very loud, blowing systolic murmur. At the base the second pulmonary sound seemed to be louder than the second aortic. The peripheral vessels were tortuous and thickened. The pulse was equal at the two wrists, totally irregular. The abdomen was greatly distended. There was evidence of considerable accumulation of ascitic fluid. The edge of the liver was felt 9 cm. below the costal margin. The spleen was not felt. The neurological examination was negative.

Course in the Hospital The patient was twice bled and given digitalis but there was little if any improvement in her symptoms. Later a profuse diuresis occurred after which the edema lessened, the dyspnea was less oppressive and the patient became more comfortable. However, this improvement lasted but a short while, soon she was just as much swollen as before, her breathing was difficult and she became quite drowsy following the liberal administration of ammonium chloride. On October 27 she began to vomit, she rapidly grew worse and died later that day.

Laboratory Examinations

Blood Count Hgb 115 per cent, R B C 5,040,000, W B C 10,000

Wassermann reaction on the blood serum was strongly positive

Blood chemical studies

	NPN	CO ₂	Plasma Prot
October 12	34 mg per cent		
October 18	34 mg per cent	56	6.8 gm
October 21	60 mg per cent		6.5 gm
October 24		27.7	

Spinal Puncture Colorless fluid 2 cells Negative Pandy Negative Wassermann reaction

Urine Specific gravity 1.009 to 1.020 No sugar, albumin—a trace A small number of leukocytes and an occasional cast in the sediment

The temperature varied from 96° to 100°

The pulse rate varied from 80 to 140

Electrocardiograms

October 18, 1935 The dominant rhythm is nodal There are extrasystoles occurring at every second beat giving rise to a typical bigeminal rhythm There are occasional paroxysms of extrasystoles arising from a different ectopic focus giving rise to runs of paroxysmal ventricular tachycardia at a rate of 125

October 27, 1935 Auriculo-ventricular nodal rhythm Dextrogram Nodal tachycardia

Here we have a characteristic instance of mitral stenosis in a woman 65 years of age, the symptoms first appearing late in life Under these circumstances we are seldom wrong in concluding that the lesion is the result of a former rheumatic infection However, in this instance the scarred appearance of the valves as seen at the postmortem examination resembles much more closely the results of a bacterial than of a rheumatic infection I do not pretend that the distinction can be made with confidence although I think the evidence makes the conclusion highly probable

Anatomical Diagnosis Mitral stenosis and calcification Cardiac hypertrophy Chronic passive congestion of viscera Syphilis (Wassermann) Arteriosclerosis Localized atrophy of kidney from arterial sclerosis Hemorrhages in urinary bladder

Dr S Jarcho's note on the heart The heart which weighs 550 gm is distinctly larger than normal There is perceptible dilatation of the right auricle The tricuspid valve presents a moderate degree of fibrous thickening along the line of closure especially marked on the anterior leaflets The chordae tendineae are opaque but not appreciably shortened There is distinct hypertrophy of the right ventricle No changes are found in the pulmonary cusps The left auricle is markedly dilated and moderately hypertrophied The endocardium is thickened but no discrete auricular patch is seen The mitral orifice is much narrower than normal and is fixed by the calcification of part of the valve When the valve is opened its edge is seen to have formed a thickened shelf with rounded edge, irregular, rough calcified masses are found at intervals along the valve The chordae tendineae are greatly shortened They are opaque and end without ramifying The endocardium over the apices of the papillaris muscles is distinctly opaque and the papillaris muscles themselves are much broader and thicker than normal There is distinct eccentric hypertrophy of the left ventricle The aortic cusps are very little thicker than normal but are fused for approximately 4 mm along the respective commissures The corpora arantii are not altered No verrucae are seen The myocardium is somewhat flabby and contains a very few inconspicuous scars

Microscopical Notes Section through the left ventricle, left auricle and mitral valve shows thickening and fibrosis of the valve and of its base with no signs of active inflammation The auricle is thickened in the endocardium and myocardium The latter shows mononuclear infiltration but not characteristic of Aschoff bodies Similar infiltrations are encountered in the epicardium which in addition is slightly scarred The ventricular myocardium shows a few perivascular scars and one vascular collection of round cells

Additional section shows dense hyaline thickening of the mitral valve and a small area of calcification The myocardium presents scattered tiny mononuclear infiltrations which are not numerous and not regularly perivascular The coronary vessels show very slight intimal thickening

Other sections taken through the anterior papillaris muscle, left ventricular and auricular ring, the intraventricular septum and right ventricle and pulmonary valve show a few tiny myocardial scars There is no evidence of active inflammation

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THE PSYCHO-BIOLOGY OF BREATHING¹

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THIS paper deals with what I have called the psycho-biology of breathing and its relation to diseases of the respiratory system. In it I have attempted to review the essential physiological facts of respiration and to indicate, when possible, links between our physiological and psychological knowledge. The connections will not always be obvious, but it seems a sound method of procedure to begin with known facts in each field and to try to bring them into relation with each other.

It may be objected by some that the laws of the body do not govern the laws of the mind—that the chasm which separates these two hemispheres cannot be bridged and certainly not by arguments based on analogy. I suspect that the split exists partially within us—is part of our own subjective ambivalence which we project on to the material under investigation and that even such divergent technics of inquiry as physiology and psychoanalysis are not so remote from one another as certain purely fortuitous circumstances have made them appear to be.

The method of psychoanalysis has contributed much to our understanding of neurotic disorders. It has provided us also with an entering wedge into some of the more obscure etiological problems of so-called functional and organic disease. But no one will deny that our knowledge is still in the form of first and rough approximation. We must try, as Santyana used to say "to define the limits of our ignorance." Nor need there be any quarrels between so-called organicist and functionalist—if that is the proper title to give his adversary. No one has a sole proprietary right to explore the secrets of nature, and each man must select the method of study that is congenial to him.

Let me now proceed to more practical matters.

A young European girl of aristocratic origin and background made up her mind against her parents' will to go to a university. She had always been a somewhat shy, reticent, easily depressed child readily inclined to tears, and rather solitary. There were many difficulties at home. The parents were not happily married. There was much friction in the atmosphere and little love, although her mother was constantly concerned with the daughter's welfare. The girl had outspoken artistic interests. She loved music, the theatre and had a respectable talent for drawing. She was on the other hand greatly interested in languages—wavered indeed between the two interests. This was a source of conflict not only in her but between her parents and herself. Finally she decided to pursue the study of languages and only after much persuasion and against great resistance could she win her parents' unwilling consent. They were by no means liberal with her in financial matters so that at the university she lived

* Received for publication May 6, 1937

in modest isolation. In the course of the second semester she began to realize that academic work was not giving her the release and satisfaction she had hoped for. Naturally this made her very unhappy but she tried with all her might to push through her plan to study, if only not to be upbraided by her father. She dragged along until the close of the semester hardly able to follow the lectures properly.

During the holidays she returned home only to hear reproaches because she looked so badly and because of her moods. She was sent to a doctor who found nothing. Constantly she was assailed by doubts as to the wisdom of further pursuing her studies. After a most unpleasant scene with her parents she became depressed and then began to cough. This again took her to the doctor who could find nothing. But the cough persisted. Upon returning to the university she consulted a specialist who at first found, as we say, nothing in her chest, but repeated examinations and roentgen-ray studies disclosed an incipient process at the right apex.

The second case I wish to describe concerns a man in his early thirties, always in excellent health, in good financial circumstances and happily married to a young woman also apparently in perfect health. During her untroubled pregnancy the husband pursued his usual business activities, was much engaged in sports, indeed even rode in steeple-chases. The wife's delivery was difficult and shortly thereafter she began to fail from what was subsequently proved to be a hydatid mole. Her illness lasted about a year when she died. The husband had not given up hope of recovery until a few weeks before the end, and in spite of his intense worry he continued in good health. As soon as the hopelessness of her condition became clear to him he began to feel badly, became depressed and quite lost his joy of living. After his wife's death his depression grew worse. Within a few weeks he had a slight pulmonary hemorrhage which he himself did not relate to a disease of the lungs, as such a possibility had not occurred to him. Upon examination, however, the diagnosis of phthisis was established.

These two abstracts of case histories are taken from a book by E. Stern¹ called "*Die Psyche des Lungenkranken*" which discusses wisely and sympathetically such problems as the reaction of patients to a diagnosis of pulmonary tuberculosis and to sanatorium life, the relationship of doctor and patient in chronic illnesses, the psychic factors in the etiology of tuberculosis. He includes a series of skillful vignettes of patients' lives in which are described, as in the ones which I have reported, long periods of tension, ambivalence and frustration which lead gradually to fatigue states, hopelessness and depression and in which the denouement is the discovery of an apical process, with a temporary resolution of the conflict by sanatorium treatment.

An extensive literature has sprung up in this field. Within the past five years the Quarterly Cumulative Index has published a new subheading "*Mental Aspects*" under Tuberculosis. Naturally we do not know what mechanisms are involved here—nor how states of tension and conflict prepare the body for the invasion of the tubercle as they appear to do. It is of importance in the first instance to establish the fact of such relationships before essaying the far more complex problem of explaining them. This first step then is a practical point of departure—a more complete and psychiatric, if you will, anamnesis of patients suffering from incipient pulmonary tuberculosis.

What we observe in these life histories is a coincidence of events. Per

haps it would help us if we dismissed from our minds, for the moment thoughts of causality, clichés about psychogenic and somatic disease or functional versus organic and looked upon these examples and upon others, which I will present as simultaneous physical and mental phenomena. From a metaphysical point of view as well as from that of modern physics the question has been raised as to whether the discussion concerning cause and effect about which we talk with so much assurance and dogmatism has in it any inherent logic other than one of temporal and statistical relationship. And so I should like to stress as our point of departure the idea of *coincidence* the coincidental happenings in the realm of the mind and of the body in relation to certain specific inner trends and outer situations. This mode of orientation toward our patients is important as it will affect our clinical judgment both in diagnosis and treatment.

I have dealt here with pulmonary tuberculosis first because it represents one of the most important of the diseases of the respiratory apparatus, secondly because problems of pulmonary ventilation may have an etiological bearing on the location of the lesion. If psychological determinants play a part in the occurrence of this disease it is reasonable to shift our ground for the moment and to look upon the phenomenon of pulmonary ventilation from this point of view as well. Speaking teleologically breathing is designed to supply the tissues with oxygen. This function is so vital to survival of the organism that we may expect to find that forces voluntary and involuntary, reflex chemical, homeostatic as well as affective, combine to insure its perfect performance.

Breathing is in more than one sense a twofold function. It is usually thought of as consisting of an external and internal process. External respiration has to do with bringing the organism into gaseous equilibrium with its outer atmospheric environment. Internal respiration is concerned with the transport of gases in the blood stream and their diffusion to the tissue cells. The exchange of gases takes place at the surface of the respiratory epithelium whether the air properly warmed and moistened has been brought after its passage through the upper respiratory tract. Here we see a rough analogy to the preparation of food in the mouth before it passes down the gullet into the stomach. I shall refer again to this analogy.

Breathing is normally adjusted to maintain a fairly constant composition of the alveolar air, because the alveolar air regulates the tension of gases in the arterial blood. Enough fresh air has to be introduced into the alveoli to replace the oxygen taken up by the blood, and to get rid of the CO_2 which has come out of the blood. The venous blood which comes to the lungs gives off CO_2 and takes up oxygen until it comes into equilibrium with the air in the alveoli. The tension of gases in the arterial blood is therefore normally about the same as in alveolar air. As we shall see later this reciprocally related process of oxygen absorption and CO_2 elimination not only insures adequate ventilation of the blood and tissues but also affects

the function of the respiratory center which is extraordinarily sensitive to changes in tension of gases in the blood

Embryologically the pulmonary respiratory apparatus develops from the hind part of the ventral wall of the head gut. Immediately behind the thyroid gland a median groove, the rudiment of the trachea, is detached from the gullet. From its hinder end a couple of vesicles develop—the simple tubular rudiments of the right and left lungs. As the respiratory apparatus is genetically and structurally related to the gastrointestinal tract, so its function seems to present an analogue of the latter. I do not mean to imply that the analogy of function derives from their common site of origin though this is an interesting field for speculation. However, both systems are concerned with the incorporation of certain substances of the external environment, with the transport of these substances to the tissue cells and with the excretion of certain products of tissue metabolism. Both digestive and respiratory systems seem susceptible to similar derangements, for example to spasms, to forced expulsion, to changes in secretion and both may become pathways for the entrance of infectious organisms. If Alexander² is correct in his assumption that the gastrointestinal tract may act out certain emotional trends having to do with ingestion, retention and elimination it is conceivable that an organ system presenting aspects so closely parallel embryologically and functionally to it can exhibit similar responses for embodying similar trends. It remains, however, for future scientific inquiry to explore the problem of psychological engrams as it has undertaken to do with physiological ones.

We have just seen that the respiratory apparatus in its rudimentary embryological form consists of a system of simple tubes. From the phylogenetic point of view this same fact holds. In the lower forms, as for example the insectivora, there are no lungs but tracheae through which atmospheric oxygen passes by simple diffusion. It is believed that respiratory movements begin at that point in the phylogenetic scale where the size of the organism and the length of its tracheae no longer permit adequate ventilation at the existing partial pressure of atmospheric oxygen. An interesting parallel to this concept can be observed in man, whose respiratory movements may disappear when he is placed in an artificial environment in which atmospheric pressure is caused to fluctuate rhythmically above and below normal pressure. Again we are confronted by an analogy with the gastrointestinal system. The fetus is nourished passively by diffusion and osmosis through the chorionic villi—only later after birth to use actively its sucking and swallowing mechanism for the ingestion of food. From a phylogenetic point of view we see in the lower forms, such as protozoa, nourishment occurring by osmosis and diffusion and only much later the differentiation of gastrointestinal tracts and the establishment of mouth parts equipped for sucking, biting, chewing and swallowing.

In the field of psycho-pathology we are familiar enough with patients

who refuse to eat even to the point of starving themselves to death. Similar reactions to breathing are not so common but are by no means unheard of. One needs to think only of the stubborn angry child who holds his breath in a temper tantum to the point of cyanosis, of the Sudanese negro who can die of asphyxia by holding his breath, and of the common and ancient form of suicide by strangulation or hanging, which like other forms of suicide is thought to express certain unconscious determinants.

As there is an analogy in the structure and function and in what might be called the psycho-pathological equivalents of these two systems so also are there certain linguistic forms the use of which suggests parallel origins. I shall mention only the fact that deep labored breathing of diabetic coma and acidosis is sometimes described as "air hunger." Many individuals during periods of tension or excitement actually swallow air.

Psychoanalysts are familiar enough with these substitutions of one organ system for another and of what appears to be—perhaps because of our lack of understanding—the welter and confusion of unconscious thought. The breath, for example, may take on the meaning of food and both may be related to fantasies of impregnation. Words may be feces, the voice the phallus. Bizarre as these interpretations may sound they are in fact not interpretations but what our patients often tell us if we are willing and able to listen to them.

Continuing with the theme of organ displacement we are familiar with vasomotor changes such as blushing and the engorgement of the erectile tissue of the nasal turbinates, which are related to emotional disturbances, also with so-called vicarious menstruation and with the treatment of dysmenorrhea by applications to the nasal mucous membrane. Whether this therapeutic procedure is founded in fact or fantasy I do not know. Frequently we encounter the so-called hysterical globus phenomenon which appears also to be a displacement and often to be related to fantasies of oral impregnation. I had recently the opportunity to observe one in *statu nascendi* and since the respiratory system was at least subjectively involved I shall describe it.

A woman of 25, married but childless, who is suffering from a severe mixed neurosis in which anxiety states and obsessional ideas predominate, was recounting a nightmare to me. She could not recall its content—only the fact that she felt an enormous weight on her chest and that she was unable to get her breath or utter a sound. This is a familiar enough setting for nocturnal terror. While she was talking the feeling returned. She lay quite motionless and said that she felt a great weight pressing on her chest as if she were unable to breathe. She then said "Aren't there stories about cats lying on babies' chests and sucking their breath away?" This patient was brought up in intimate association with a pet cat who in many respects was a rival preferred by her mother. She is the only patient whom I have seen to whom an animal has played the rôle of sibling and who has in many respects identified herself with a cat. She constantly dreams of a mother cat and kittens, of kittens being born in the toilet and of poor, starved, thin, homeless kittens. When she passes a stray cat on the street she is overcome with a desire to take it

home and mother it. The next step in the story is she now felt the weight lying on her chest was a cat. This was in no sense an hallucination. It was a fantasy. She continued to feel breathless and then told me she felt the cat was inside her chest. After awhile the feeling of substernal oppression passed and the patient then complained of a lump in her throat which made her feel as if she were strangling. This in turn passed off and she again breathed quietly and easily. A few days before this experience she told me of a dream in which some birds fell over as if dead, whereupon little birds appeared to hop out through the bigger birds' chest walls. She has a constant fear of death as she has of sexuality and childbirth which are closely associated in her mind with the idea of dying. Paradoxically enough she has a strong suicidal drive, as if indeed she wanted to jump into the lake to escape the rain.

The feeling of being unable to take a deep breath, i.e. dyspnea, is commonly encountered in anxiety states, indeed the sensation itself undoubtedly gives rise in some individuals, though not in all, to feelings of anxiety. Dyspnea is properly speaking a subjective symptom, not an outward sign. It has been defined by Means³ as "the *consciousness of the necessity for increased respiratory effort*". It will occur, as Means says, whenever the respiratory mechanism cannot with ease function to the extent that bodily processes require. It is an interesting fact that consciousness is directed to the thorax or diaphragmatic region while the cause of the difficulty may be either in the lungs or in some far distant part of the body. The most common cause of dyspnea is physical exertion.⁴ The increased pulmonary ventilation is then the result of increased metabolism. This does not lead to any distressing symptoms until the demand for oxygen and elimination of carbon dioxide is greater than the lungs can perform with comfort. Thyrotoxicosis and febrile states may produce a similar type of dyspnea due to excessive metabolic demands. A different mechanism, yet one occasioning the same subjective sensation, may result from anemia, anoxemia, changes in the acid-base equilibrium of the blood and tissues, or decrease in cardiac output. In each one of these the disability and distress are referred to the breathing apparatus—just as it is in those conditions such as pneumonia, congestive heart failure, pulmonary fibrosis, emphysema, and bronchial asthma where the fault actually lies in decreased efficiency of the pulmonary bellows and is associated with reduction in vital capacity and pulmonary elasticity. The localization of respiratory distress in the region of the diaphragm even when the pathological lesion is remote is an interesting phenomenon. It seems almost like a conditioning or like a projection, as if the patient were saying "I can't breathe easily, therefore there must be something wrong in my chest". Perhaps, however, the sensation is experienced where it is because existing nervous pathways can convey it nowhere else. It is apparently a well canalized one, for many sensations of excitement and anxiety are felt in the same zone. Those of us who were in the war saw numerous cases of so-called *neuromuscular asthemia* or *disordered action of the heart* in which shortness of breath played a prominent part. I remember an enormous black negro in a white night shirt sitting up in bed and breathing at the rate of 120 per minute with nothing abnormal disclosed.

on the physical examination to account for such a disturbance. In some of the more severe cases of this sort pronounced cyanosis appeared and even collapse from what was thought to be exhaustion of the respiratory center. Very often, however, during sleep or hypnosis the respiratory rate returned to normal. That the condition was associated with an acute anxiety state with suppression of affect is not improbable. The physiological explanation given for this type of rapid and shallow breathing is that "the normal reflexes are preternaturally hypersensitive". Breathing is, to be sure, only partially controlled by reflex mechanisms. In the control and regulation of the rate and depth of breathing its twofold character is again in evidence. Its regulation is partly nervous, partly chemical. It is partly reflex, partly under voluntary control. In this respect it differs somewhat from the other two great vegetative systems, the cardiovascular and the gastrointestinal, and resembles more nearly the mechanism of the sexual function. It is perhaps because it represents a meeting point of conscious and automatic activity that it so easily lends itself to an expression of emotional tensions and disturbances.

The impulse to breathe arises in the so-called respiratory center which is located somewhere in the medulla oblongata about at the level of the *striae acousticae*. This locus was first identified in 1811 by Le Gallois.⁶ The center apparently discharges at a constant slow rate sending impulses to the intercostal muscles along motor fibers of the spinal nerves and to the diaphragm through the phrenic nerves. Recently these rhythmically discharging impulses have been studied and graphically recorded in the cat by Adrian.⁷ Their origin is of course unknown but they appear to resemble the so-called Berger waves from the cerebral cortex. The activity of the center is exquisitely sensitive to changes in the H-ion concentration of the blood and the lymph which bathes it and perhaps specifically to CO₂ and also, of course, to oxygen want. Since oxygen want constitutes a profound threat to the integrity of the organism, more especially to the functioning of cortical and autonomic centers, it is probable that the feeling of anxiety and panic induced by asphyxial states serves as a danger signal to the individual. We are familiar with Freud's concept of anxiety as a danger signal. Whether anxiety, more specifically neurotic anxiety, is related to anoxemia as Deutsch⁸ has intimated, we do not know. This is a problem which could be investigated. McFarland and Barach⁹ have recently exposed a group of psycho-neurotic individuals to low partial pressures of oxygen. They found that these patients tolerated low atmospheric oxygen less well than a control group. There is in all probability a high degree of individual variation in this. Some individuals respond to anoxemia and shortness of breath with feelings of anxiety and others do not, perhaps depending upon their capacities to function physiologically at low oxygen tension, and perhaps also upon their earlier conditioning in respect to these states. I shall not deal here with work which has been done on the effects of low oxygen tensions on sensory

reaction times, muscular coordination, discriminative judgments, etc. I refer to observations made with rebreathing apparatus and low pressure chambers especially in relation to testing of fliers, also to observations made at high altitudes. The recent International High Altitude Expedition to the Andes¹⁰ has furnished some data which may make it possible to predict which individuals will tolerate low oxygen pressures well and which will not. This, to be sure, is a different problem from the one to which I have already referred, i.e. the relation of anxiety to anoxic states.

Chemical stimuli determine to what extent inflation and deflation will occur but probably have little influence upon the frequency of respirations. The latter is governed by a sensory reflex mechanism first described in 1868 by Hering and Breuer¹¹. Afferent sensory impulses from the lungs reach the center by way of the vagus nerves. Their existence has been demonstrated not only by cutting and freezing experiments which elicit typical slow, deep, so-called vagal, breathing, but action currents of afferent vagal impulses synchronous with respiration were demonstrated by Einthoven¹². The vagi, as the great afferent nerves of the lungs, serve in the complicated apparatus to protect them against the effects of excessive distention or collapse. They inform the respiratory center of movements of air currents and the position of the lungs, and reflexly check the depth of breathing. The chemical factors therefore control the total pulmonary ventilation, the afferent vagal impulses control the rhythm of breathing. I have not dealt here with the less understood function of intrinsic sympathetic pulmonary and bronchial ganglionic plexuses. In general, as Means¹³ says, the nervous control of breathing may be expected to secure for us that respiratory type which in accordance with the local condition in our chest or abdomen, may most comfortably supply the ventilation required for the gas exchange which our general bodily processes may happen at any time to demand.

I have described this subject of the control of the depth and rate of breathing for two reasons. First, because a recent attempt has been made by Alexander and Saul¹⁴ to relate the form of the respiratory curve to certain personality traits, second, because a discussion of the nervous control of respiration leads naturally to a consideration of asthma in which occurs a reflex stimulation of the smooth muscle of the bronchial wall through vagal broncho-constrictor fibers and in which an emotional element plays a rôle of major importance.

Regarding Alexander and Saul's work, I have, to be sure, seen only an abstract. They believe they have shown that a certain correlation exists between the form of the respiratory curve and certain libidinal trends. That the respiratory curve is influenced by anxiety, by tension and even by a specific personality factor, I am quite ready to believe. But to establish the fact that a correlation exists between the form of the respiratory tracing and specific instinctual drives would require a large statistical material. Alexander and Saul are quite aware of this. They present their conclusions with

appropriate caution and modesty I am glad to learn that Deutsch and Finesinger¹⁵ are also engaged in investigating this problem with particular attention to the influence of induced affective states on the form of the respiratory curve

Turning now to the subject of asthma I should like to summarize certain findings concerning it in the psycho-somatic field That asthmatic attacks are often closely bound to certain specific life situations is now common knowledge Psychotherapy, after other methods of treatment have failed, has in some individuals brought about the disappearance of Charcot-Leyden crystals, Curschmann's spirals and even of eosinophilia from the sputum and blood I refer to a series of cases reported upon by Moos¹⁶ Hansen's¹⁷ investigation led him to the view that the psychological situation has much to do with the reactivity which some patients exhibit to specific antigens to which they are sensitive Moreover he says "I cannot escape the impression in many cases that not infrequently a seemingly causal psychic alteration may be only coordinated with the somatic reaction, and that both are dependent on a mysterious third factor that escapes our detection It seems to me, for example, that not infrequently certain asthmatic individuals show to a more or less marked degree symptoms of manic-depressive disease, and that asthmatic attacks predominate in attacks of depression"

Support of Hansen's contention is furnished by Saxl¹⁸ who reports the case of a patient, who had suffered from migraine since early youth and had been subject to fluctuations of mood He was seized with attacks of bronchial asthma during the involutional period Some years later, perhaps precipitated by a further psychic trauma, he developed a manic-depressive state in the course of which five exacerbations were observed An attack of asthma subsided each time previous to the acute exacerbation of psychosis, only to return with its disappearance Oberndorf¹⁹ reports the analysis of an asthmatic in which he believes it was shown (1) that psychological stimuli set the attacks in motion, (2) that the so-called specific allergic determinants had nothing to do with the attacks, and (3) that after treatment the asthmatic attacks were substituted by emotional outbursts quite like manic episodes The patient, after treatment, ate chicken, corn and cabbage freely and was able to tolerate the presence of dogs and cats To all of these she exhibited positive skin reactions Fenichel²⁰ has attempted a more detailed description of the psycho-dynamic situation in asthma—stating that asthma is not an hysterical conversion symptom and that the asthmatic between attacks behaves like an obsessional neurotic In his book in which he devotes some ten pages to the subject, Fenichel places asthma between stuttering and psychogenic tic He assumes the existence of intrinsic respiratory eroticism and reduces the psychological process in asthma to a formula, of the validity of which I am on principle rather skeptical As to the therapy of asthma, Fenichel believes that the analyst's task is the radical treatment of the pregenital psychological structure which he believes underlies the

symptom. Quite properly Fenichel also mentions the intimate relationship that exists between anxiety and the function of respiration. In this connection he discusses the views of Hainik²¹ who finds the fear of suffocation a widespread phenomenon and relates it to castration anxiety of which he believes it to be a distorted expression. One of his patients, for example, imagined that the analyst might cut off his air supply by means of scissors. The second point derived from Hainik is that fear of being smothered underlies every fear of death and is in general the most archaic content of anxiety. He believes that this feeling, which may be experienced at the time of suckling, remains connected unconsciously with every later experience of a dangerous situation. I have at present under observation a young man who develops deep gasping respirations whenever his anxiety is aroused by matters touching on his social or economic inadequacy. All his life he has suffered from an acute sense of anxiety in any situation in which there was any suggestion of smothering—for example, if any one in fun would put a pillow on his head. The intimate relationship which exists between anxiety and respiration suggests the possibility that the constant variations in respiratory function are based in part, at least, upon constant unconscious responses to anxiety. It is my personal observation that the sensation which we recognize as anxiety is felt in the lower anterior thoracic wall and presents itself to us as a feeling of being unable to inspire freely. I suspect that it may arise in kinesthetic impulses from the diaphragm which may be related to its tonus. Christie²² believes that the incidence of respiratory disorder in neurosis is much greater than is generally supposed and that tracings taken by means of an ordinary recording spirometer are of value in the diagnosis and differentiation of certain types of neuroses. His cases fell into two groups: anxiety neuroses with irregular shallow type of respiration, and conversion hysterias, with a tendency to hyperventilation. This latter occurrence is consistent with sighing respiration which I have mentioned and to which Baker²³ has recently drawn attention. A thorough investigation of pulmonary volumes would be of interest in this connection.

As might be expected, the idea of "birth trauma" has found its way into discussion of the etiology of asthma. Freud has challenged the value of this hypothesis admirably in his recently translated "Hemmung Symptom und Angst." May I quote "The principal objection to be raised against it, however, (i.e. the birth trauma) remains the fact that it hangs in mid-air, instead of being based upon verified observation. For no trustworthy investigation has ever been carried out to determine whether difficult and protracted birth is correlated in indisputable fashion with the development of neurosis—indeed, whether children whose birth has been of this character manifest even the nervousness of earliest infancy for a longer period or more intensely than others. If the assertion is made that precipitate births, those easy for the mother, may possibly have for the child the significance of a severe trauma, then *a fortiori* it would certainly be necessary that births

resulting in asphyxia should produce beyond any doubt the consequences alleged. It seems an advantage of the Rankian etiology that it postulates a factor capable of being checked empirically, but as long as such a check has never actually been undertaken, it is impossible to estimate its real value." There is of course no reason why such an investigation could not be undertaken with special reference to asthmatics.

Closely related to this psychoanalytical hypothesis are certain recent physiological studies made in England by Barcroft²⁵ and in this country by Rosenfeld and Snyder²⁶ at the Johns Hopkins Medical School. These investigators have studied intra-uterine fetal respiratory movements. Barcroft's work began several years ago with an effort to answer the question "What sets off the birth process?" By a study of arterial oxygen saturation of goat fetuses he believes he has demonstrated increasing anoxemia as the fetal circulation no longer supplies the needs of the growing organism. A point is reached when, as Barcroft²⁷ put it "It gets so stuffy that the fetus moves out." If this is true then the amniotic sac is perhaps not the Nirvana which some psychoanalysts have led us to believe. States of tension and frustration may already be experienced in utero, and birth is not into a vale of tears, nor the prototype of all subsequent traumas, but rather a happy release. Barcroft demonstrated cinematographically the existence of rhythmic respiratory movements in fetal sheep and goats beginning as early as the thirtieth day, but curiously enough disappearing during the course of gestation. The occurrence of intra-uterine respiratory movements is not a newly discovered fact, having been observed by Preyer²⁸ as long ago as 1885. It received scant attention, however, until recently. Rosenfeld and Snyder have improved upon Barcroft's technic by eliminating the use of general anesthetics which they discovered depressed or completely inhibited intra-uterine respiration in the fetuses. Their observations were made on rabbits after section of the lumbar cord under local anesthesia. Fetuses within the intact uterus exhibited spontaneous respiratory movements characterized by rhythmic excursion of the thorax and abdomen. Although shallower, they resemble qualitatively the respiratory movements observed after birth. There is great variation in respiratory activity among different fetuses in the same uterine horn, some may be quiescent, others respiring at independent rates up to 60 per minute. No evidence was found that stimulation of fetal respiration occurs from oxygen want nor indeed from the administration of CO₂ to the mother. They regard the onset of post-natal respiratory activity not as an event initiated abruptly at birth but rather as a transition from the type of respiratory movement discernible during intra-uterine life. They do not support the view of Barcroft that the first breath of a newborn animal is caused by oxygen want. To be sure cyanosis often occurs in the newborn as the result of prolonged labor and the use of anesthetic agents in the mother—but, as has been said, whether this constitutes a psychic trauma to the child is still unknown. In the

absence of such knowledge it hardly seems fruitful to try to explain the disordered breathing of an asthmatic attack in terms of regression to the post-natal state

The condition of oxygen want naturally leads us to a consideration of pneumonia. There is more accurate knowledge about anoxemia in pneumonia than in almost any other disease. In spite of this, I know of no serious effort to correlate psychic changes in patients suffering from pneumonia with changes in the degree of anoxemia, though there have been comments on the decrease of restlessness and subsidence of delirium during oxygen therapy.

That the morbid picture is much influenced by anxiety states—fear of suffocation—fear of death, I have no doubt. A careful study of the events leading up to the infection would be of interest, as well as a study of the productions in delirium and the effects of more active suggestive therapy. C. Widmer²⁹ was aroused to an interest in this problem by events occurring after a fire in the Swiss hamlet of Tamins in which eight of those engaged in fighting the fire after drenching and exposure came down in from one to two weeks with attacks of severe pneumonia initiated by chills and soon followed by high fever and delirium. The patients lived at great distances from each other so that the doctor could not visit them all. In order to protect them from exposing themselves during their nocturnal delirium he was led to adopt the emergency measure of getting the patients out of bed at night and having them dress. He found to his amazement that the active delirial symptoms disappeared and that there occurred simultaneous clinical improvement. Apparently this experience caused him to investigate in the succeeding 10 years some of the psychological disturbances which he regarded as characteristic of pneumonia and which in his opinion were not related to the deliria of high fever nor to toxic exhaustive states. He found alteration in what might be called the integration of perception—a disturbance in the recognition of place, position, space, distance, division, rhythm, number, movement. This, according to Widmer, is the basis of the delirial state which may be present early in the disease and may be unrelated to the height of the fever or to any evidence of meningeal involvement. Since the patient's memory for recent events and his superficial contact with his environment may be unimpaired the existing delirium may at first escape detection. Widmer essayed to correct this state of confusion not by direct conscious psychotherapy since he found his patients lacking in insight and quite inaccessible, but by the expedient of getting them out of bed. Sometimes he had them sit in rocking chairs for as much as from four to six hours a day, even letting them take a few steps. By these and various other maneuvers he attempted to bring them back to a more normal relationship to their environment. He states that the procedure far from doing the patients harm led to normal sleep, to disappearance of delirium, to improvement in blood pressure and to moderation of toxic manifestations. Widmer's observations, of course, need corroboration, although it would

require some temerity to repeat them in this country where it is customary to keep the convalescent from pneumonia at rest in bed for at least a week after his temperature has returned to normal. Still I think it is apparent that these experiences if they are correctly reported are not without interest

In the beginning of this paper I spoke of the unwisdom of advocating such concepts as *psychogenic versus organic* as applied to the etiology of disease. It is my belief that any disease from hysteria to carcinoma or better any diseased individual may be studied legitimately and with profit by methods both psychological and organic. What we discover with these methods will be different sets of facts, in the one instance psychological facts, in the other, facts which have anatomical, chemical or physiological bearings. To correlate these will always be difficult—perhaps will be looked upon for the present as a *tour de force*. But such efforts seem to me to be of value. Our attitude toward disease is changing. It is no longer satisfactorily explained as a catastrophic invasion by noxious agents, a belief handed down to us not by bacteriologists alone but by our more primitive animistic ancestors. We know now that it requires more than the tubercle bacillus to make a man tuberculous, more than a specific antigen to produce an asthmatic attack and more than pneumococci to precipitate an attack of pneumonia. The other ingredient in the disease state was then thought to reside in the “reaction of the host,” by which was meant in his humoral and immunological defenses. There is now a growing body of evidence which leads to the belief that psychic influences as well play an important part in the process of falling ill, and that disease be it infectious, allergic, functional, organic or degenerative has its developmental history in which the whole personality is involved. To cultivate this field we must create new methods of personality study aided by the insight which psychoanalysis has given us.

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CASE REPORTS

MARKED UREMIA WITH RECOVERY, REPORT OF A CASE*

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CASE REPORT

J F, a 29-year-old white woman, was admitted to the Surgical Service of the Cleveland City Hospital on September 12, 1933

According to the patient's history her last menstrual period had occurred on July 8, 1933. Having missed her August period and believing herself to be pregnant she had attempted to produce an abortion by the use of various oral medications, the exact nature of which we were unable to determine. Failing in this attempt an abortion was induced on September 7, by packing the vagina with gauze. The pack was removed after one day and was followed by rather profuse vaginal bleeding. Twenty-four hours later the patient had a severe chill and felt feverish. She began to vomit rather copiously and it was called to her attention that her eyes had become yellow in color. These symptoms became increasingly severe until the time of her admission to the hospital.

The past history was negative except for four induced abortions during the past eight years, several of them followed by chills and fever. The patient had four living children.

Examination showed the patient to be well-nourished and acutely ill. The skin and sclerae were definitely jaundiced. There were no visible petechiae. The heart and lungs were normal. The blood pressure was 110 systolic and 60 diastolic. The abdomen was negative except for the liver which was just palpable at the costal margin. The spleen was not palpable. Pelvic examination revealed the cervix to be lacerated but firm. The uterus was enlarged, boggy and in a posterior position. There was tenderness in both fornices on motion of the cervix. There was no peripheral edema and the reflexes were physiological.

The temperature on admission was 37.8° C, the pulse 90, and the respirations 20. The blood urea nitrogen was 183 mg per 100 cc, the creatinine 18.6 mg per 100 cc, the carbon dioxide combining power 20 volumes per cent, the icteric index 63, and the hemoglobin 65 per cent (Sahli). A blood Wassermann was negative.

The clinical impression on admission was that of an incomplete abortion, and a toxic hepatitis and nephrosis with uremia. The latter lesions were attributed to the ingestion of an unknown drug.

Two days after her admission to the hospital the patient signed her release and was discharged against advice.

The patient was readmitted, this time to the Medical Service, on September 23, 1933, eleven days after her original admission. Her condition during this interval had become progressively and rapidly worse. At this time the history was obtained from the patient's husband that the abortion on September 7, 1933 had been attempted by placing two bichloride of mercury tablets against the cervix and packing the vagina with gauze. Samples of the oral treatment (Savatan capsules in their original box, several of which were missing and one broken in half) were also submitted.

* Received for publication November 18, 1936
From Cleveland City Hospital, Cleveland, Ohio

Examination at this time revealed the patient to be deeply jaundiced. She was extremely ill, toxic, disoriented, and had a watery and bloody diarrhea. The physical findings were not of great significance. The respirations were regular and very deep in character. The liver was not palpable. There was slight bilateral costo-vertebral tenderness. The temperature was 37° C, the pulse 90, and the blood pressure 110 systolic and 64 diastolic. There was no pericardial friction.

The laboratory findings on the day of this admission showed that the blood urea nitrogen was 352 mg per 100 cc (checked), the creatinine 24.3 mg per 100 cc (checked), the uric acid 14.4 mg per 100 cc, and the CO₂ combining power 14.5 volumes per cent.

The clinical impression on this admission was uremia due to bichloride of mercury poisoning, with hepatitis and nephrosis.

During the 10 days after admission the patient's condition remained critical. She was disoriented the greater part of the time. Her diarrhea continued with four to seven stools daily. Her urinary output when measurable varied between 250 cc and 750 cc a day. She developed a bilateral suppurative parotitis which required incision and drainage, and a bilateral acute otitis media which required myringotomy. Treatment consisted of usual routine measures for bichloride of mercury poisoning, 4000 cc of normal saline solution daily by clysis, imperial drink, sodium thiosulfate, and glucose given by mouth and intravenously. The anemia which became rather marked responded well to a 50 per cent solution of ferric and ammonium citrate. After two weeks her improvement was slow but steady and there were consistent changes in the urinary and blood chemistry findings. On 11-14-33 her blood urea nitrogen and creatinine were normal and the urine negative, with low specific gravity. Phenolsulphonephthalein excretion was 45 per cent in two hours and the average of two Van Slyke urea clearances (maximum clearance) was 63 per cent. A Mosenthal test run the next day showed average specific gravity of 1.014 for the day and the same figure for the night specimen. On 12-9-33 her blood urea nitrogen had risen slightly to 19.8 mg per 100 cc and a repeat urea clearance determination was 34 per cent of standard and 39 per cent of maximum. She was discharged from the hospital on 12-11-33, three months after her first admission, having nearly regained her normal weight. The chart gives the blood and urine findings during her hospital stay.

On 9-13-35 she was again admitted on the Obstetrical Service of City Hospital and was delivered uneventfully of a normal full-term child. Her post-partum course was not remarkable. Physical examination at this time showed no significant findings. Her blood pressure was 102 systolic and 64 diastolic. The urine was negative for albumin, sugar, cells and casts. The specific gravity was 1.008. The patient left the hospital by release before kidney function studies could be performed.

The patient was seen personally in February 1936, two and one-half years after her original admission. She refused further follow-up studies but stated that she had been quite well and able to do all of her own housework.

A search of the literature has failed to reveal a case of such marked uremia with recovery, and we feel that recovery here has been adequately proved by the ability of her kidneys to withstand pregnancy. Selman and Lengier,¹ from this hospital, have reported a case of asthmatic shock which recovered after developing a blood urea nitrogen of 142 mg per 100 cc and creatinine of 15.4 mg per 100 cc. Our case showed a much more severe blood picture, while the blood urea nitrogen is the highest seen by us in some 25,000 determinations.

We have no proof that this is a case of mercury bichloride poisoning. Only one sample of urine of less than 100 cc was examined for mercury on 9-26-33 and none was found. One would not expect to find it in such a small quantity of urine, particularly since the absorption and excretion from the vagina would

both be rapid, and small amounts of mercury are more toxic by this route. This same sample was negative for leucine and tyrosine crystals. Montzka² has reviewed poisoning with mercury by the vaginal route and reports a fatal case. Mintz³ has reported that 7.5 grains of mercury bichloride were fatal. The history here indicates double this dose was used.

The other possible etiological factor is the Savatan. The Bureau of Investigation of the American Medical Association has kindly supplied the information that Savatan contains the ecboic oils of tansy, mint and apiol.⁴ Brenot,⁵ whose original article we were unable to obtain, has reported a case of fatal poisoning with apiol with intestinal symptoms, icterus and uremia, but the dose which is toxic (0.6 to 0.8 gm.) would be improbable here since only eight and a half of the capsules had been taken. One of the important toxic actions of this drug is on the heart, yet at no time did this patient show any cardiac abnormalities. The hepatitis, which occurred rather early to be due to mercury, might have been caused by the ecboic oils.

SUMMARY

A case record is presented of a patient with marked kidney insufficiency probably produced by mercury bichloride per vagina, who recovered sufficiently on routine treatment to undergo a normal pregnancy two years later.

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REPORT OF A CASE OF STATUS ASTHMATICUS WITH AUTOPSY

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CASE REPORT

Mrs. E. H., a housewife, aged 40, entered the University Hospital, October 16, 1935, complaining of severe asthma.

Her mother, aged 77, has arteriosclerosis. Her father died at 50 of heart trouble. One brother is living and well, no sibs have died. She has four living children, one of whom has diabetes for which insulin is taken, one child died at four of nephrosis. No allergic family history could be obtained. The patient lived in Syracuse, New York all of her life except for two trips to Florida in 1925 and 1927. In childhood she had measles, mumps, and varicella, jaundice in 1915, pleurisy twice (1918 and 1934), mild scarlet fever in 1927 with no complications. A goiter had been present for 27 years. There had been some swelling of the ankles for 11 years, most

* Received for publication November 5, 1936.

noticeable at night Since the attack of scarlet fever in 1927 she had been moderately short of breath

Previous hospital admissions 1919, Laparotomy—gall-bladder found to be normal, appendix removed 1934, Acute upper respiratory infection—asthma 1935 (March) Acute upper respiratory infection—asthma 1935 (May) Severe asthma

During her stay at the University Hospital in 1934 the following observations were made Hemoglobin 93 per cent, red blood cells 4,900,000, white blood cells 7,500, polynuclears 59 per cent, lymphocytes 33 per cent, large mononuclears 5 per cent, eosinophiles 3 per cent Other eosinophile counts were 0, 1 per cent and 5 per cent

The patient attended the Cardiac Clinic at the Syracuse Free Dispensary from July 3, 1934 to April 16, 1935 Numerous observations of the vital capacity, blood pressure and heart rate gave the following average readings vital capacity 2,475 c c, blood pressure 126 systolic and 85 diastolic, heart rate 86 The heart outlines were within normal limits and the sounds were clear She was discharged with a final diagnosis of "No organic heart disease—bronchial asthma"

She came to the Allergy Clinic at the Syracuse Free Dispensary July 31, 1934, and was under my observation until her last illness Her first asthmatic seizure occurred in September 1929, two years after an attack of scarlet fever For five years she has taken ephedrine every night and often has had to sit up in a chair The asthma was worse in winter and in rainy weather In the summer of 1934 from June to August she had considerable sneezing

More than 80 intracutaneous skin tests gave positive reactions to house dust, ragweed, feathers, wheat, lima bean, lamb and cocoa She was given advice as to environmental precautions and the elimination of suspected foods, and was treated by injections of house dust, ragweed and mixed stock respiratory vaccine At her visits to the clinic she appeared cheerful and optimistic and seemed to show some improvement but upon close questioning admitted one or more attacks of asthma requiring ephedrine practically every night At times her daughter gave her epinephrine by hypodermic She was placed upon a Rowe elimination diet for five weeks without relief On May 17, 1935, she had a severe attack of asthma, the tongue was said to be swollen and the face and hands blue She had to be carried downstairs in a rocking chair and was taken to the Onondaga General Hospital where she remained one week

Late in September 1935 she developed an acute upper respiratory infection which kept her in bed four days and caused a marked increase in the number and severity of the asthmatic attacks She became exceedingly weary and remained propped up in bed all of the time A hypodermic of epinephrine had always helped her but on October 16, she was unable to obtain relief, even from 1 c c She became faint and was sent by ambulance to the University Hospital, where she was placed on the medical service of Dr W D Ayer *

Admission examination A refined appearing woman of good nutrition and development, sitting up in bed, breathing with great difficulty, using all of the accessory muscles of respiration Pupils are equal and react to light and accommodation Some nasal discharge A few dental cavities Throat injected, tonsils cryptic Small goiter Lungs hyperresonant and filled with wheezing rales Heart enlarged to left with systolic and diastolic murmurs in the mitral area, and a diastolic blow at the left border of the sternum Sounds are regular in force, rate and rhythm Blood pressure 150 systolic and 90 diastolic Abdomen soft, operative scar present Liver and spleen not felt Reflexes hyperactive

During the five days of her hospital stay she presented the picture of continuous asthma which resisted all medication She took very little fluid by mouth and practically no food She went practically without sleep except for a few brief intervals

*I am indebted to Dr W D Ayer and to Dr E C Reifenshein, physician in chief, for the privilege of using the records of the University Hospital



Fig 1 Large bronchus (low power and high power) Thickening of mucous membrane Inflammatory reaction and dilated vessels

when she became drowsy after a hypodermic of morphine. Ether and oil per rectum were not well retained and had little effect. Continuous oxygen therapy by tent was of little service. The diastolic murmurs noted at entrance were not heard thereafter. The pulse became more rapid, the skin cyanosed, the ankles edematous and the abdomen distended. Unconsciousness supervened, the temperature reached 108° ante mortem and the patient died from exhaustion on October 21, 1935.

She received iodide by mouth and vein, calcium gluconate, inhalations of epinephrine 1-100, ephedrine gr 3/8 with amytal gr 3/4 morphine by hypodermic gr 1/8 to 1/4 with and without atropine, 14 doses, a total of 2 5/8 grains, digitalis 9 doses, 13 1/2 grains. At first 1 c c doses of epinephrine were given by hypodermic, later 0.5 c c was administered at intervals of 15 to 30 minutes. In all 114 doses were given, about 2 1/2 oz in five days. Until just before death the temperature had varied from 98.6° to 101°, the pulse from 82 to 120, and the respirations from 20 to 30.

Following are the essential features of the autopsy by Dr. Robert O. Gregg and Dr. J. Howard Ferguson. Body is that of a fairly well developed, well nourished, middle-aged woman. There is apparently slight distention of the abdomen. There is slight edema of the ankles.

Pleural Cavities. The lungs fill the cavities and meet across the midline when the thorax is opened and cover nearly the entire pericardium. There are no adhesions and no free fluid.

Thyroid. The thyroid is symmetrically enlarged, but the trachea is not depressed.

Mediastinum. Without evident lesion.

Pericardial Cavity. Contains approximately 10 c c of clear amber fluid. Pulmonary artery opened in situ is without evident lesion.

Heart. Weight 275 gm. The right auricle is markedly dilated and filled with fluid blood. The ventricles are contracted. The auricular appendages are without evident lesion. The tricuspid, pulmonary and aortic valves are without evident lesion. There is some thickening along the line of closure of the mitral valve, particularly on the anterior cusp. The coronary arteries show a slight amount of yellowish thickening and seem to be soft throughout their entire extent. On section of the myocardium the muscle is deep reddish brown in color and rather firm in consistency. There are two small areas of whitish softening in the anterior wall of the left ventricle.

Lungs. Weight of left 260 gm. Weight of right 260 gm. On section the lungs seem much more crepitant than usual. On pressure there seem to be scattered diffusely throughout both lungs numerous air-containing spaces up to 1/2 or 1 cm in diameter. The bronchi throughout both lungs, particularly in the lower lobes, are filled with thick tenacious mucus. The lungs are grayish pink in color throughout. Vessels and bronchial lymph nodes show nothing unusual.

Liver. Weight 1500 gm. The liver substance is yellowish brown in color and somewhat firmer in consistency than usual. There appears to be a minimal amount of scar tissue throughout the entire liver structure.

Kidneys. Weight 260 gm. The kidney substance is reddish brown in color throughout except for one area of rather grayish white color and firm consistency in the cortex of the left kidney. This area is approximately 1 cm in diameter and extends to the capsule. The capsules strip easily. The cortex and medulla have the usual relationship.

Adrenals. Show nothing unusual.

Aorta. Shows a minimal amount of yellowish thickening.

Anatomical Diagnosis. Bronchitis. Marked pulmonary emphysema. Probable infarct of kidney.

Microscopical Diagnosis. *Heart.* Some fatty and Zenker's degeneration of myocardium. Slight fibrosis. *Liver.* Slight fine scarring in areas. *Kidneys.* Infarction.



Fig 2 Small bronchus (low power and high power) Mucous plug filling lumen Slight inflammatory reaction No change in basement membrane

with extensive, capillary thrombosis of glomeruli, marked tubular degeneration. *Lungs* Generalized emphysema with scattered areas of slight fibrosis with some infiltration of lymphoid cells. The larger bronchi show some infolding of the mucous membrane. In some areas the goblet cells are more prominent than usual. Other areas do not appear unusual. The basement membrane throughout shows rather marked thickening and hyaline degeneration. In the sub-epithelial connective tissue there is a diffuse infiltration of leukocytes consisting of lymphoid cells, plasma cells, and eosinophiles in about equal proportions. The small blood vessels in this area are unusually prominent. There are scattered capillary hemorrhages. The mucous glands are prominent but otherwise not unusual.

The smaller bronchi and bronchioles show less infolding of the mucous membrane. The basement membrane shows only scattered areas of thickening and very little hyaline degeneration. There is some infiltration of leukocytes in the sub-epithelial connective tissue. These cells are in about the same proportions as found in the larger bronchi. The blood vessels do not appear unusual. The lumina in many places are filled to a varying degree with rather dense mucoid material containing many lymphoid cells, plasma cells, and eosinophiles in about equal proportions. There is very little crystalline material seen.

Why did this woman go into status asthmaticus which resisted all treatment and led to death within a week? The exciting cause appeared to be an acute upper respiratory infection which produced a marked increase in the severity of her asthma. It is well known that infections of this type, popularly called colds, are the *bête noire* of numerous asthmatics, who may be quite comfortable in the intervals between these bouts of infection. The general population entertains these disorders in such large numbers, especially during the colder months of the year, that probably no striking decrease in their incidence can be brought about until a form of preventive vaccination, practicable on a large scale, can be developed.

Would altered treatment have resulted in her recovery? Undoubtedly the amount of epinephrine administered was very large—about $2\frac{1}{2}$ oz. within five days. May not this have caused an exhaustion of the glycogen reserve of the body, where almost no food was consumed? Epinephrine, particularly in large amounts, may have unfavorable side effects. Doses as high as 1 c.c. which were given to her for a time, may actually be harmful and should seldom be used save in acute emergencies. From 0.2 to 0.4 c.c. is probably best for the average attack, repeated in 20 minutes or as often as may be necessary. The action of epinephrine is rapid but not sustained, hence the rationale of frequent doses which are not too large. In asthmatics who have become refractory to subcutaneous injections, intravenous epinephrine may give startling relief. Inasmuch as powerful effects may follow intravenous injections the initial dose must be very small. I have seen an attack of asthma broken in an epinephrine refractory patient by as little as 0.1 c.c. of 1-10,000 epinephrine intravenously.

Did the administration of morphine contribute toward this patient's death? She received within five days 14 hypodermic injections totaling $2\frac{3}{8}$ grains. Not many physicians have seen asthma patients die following morphine administration, and case reports in the literature are uncommon. The statement is not infrequently made that morphine is dangerous in asthma and had better be withheld, but actual evidence bearing upon its action and results is scanty. Cohen and Rudolph¹ report that they have seen five patients with acute asthma in whom death followed within a few hours after morphine administration, and

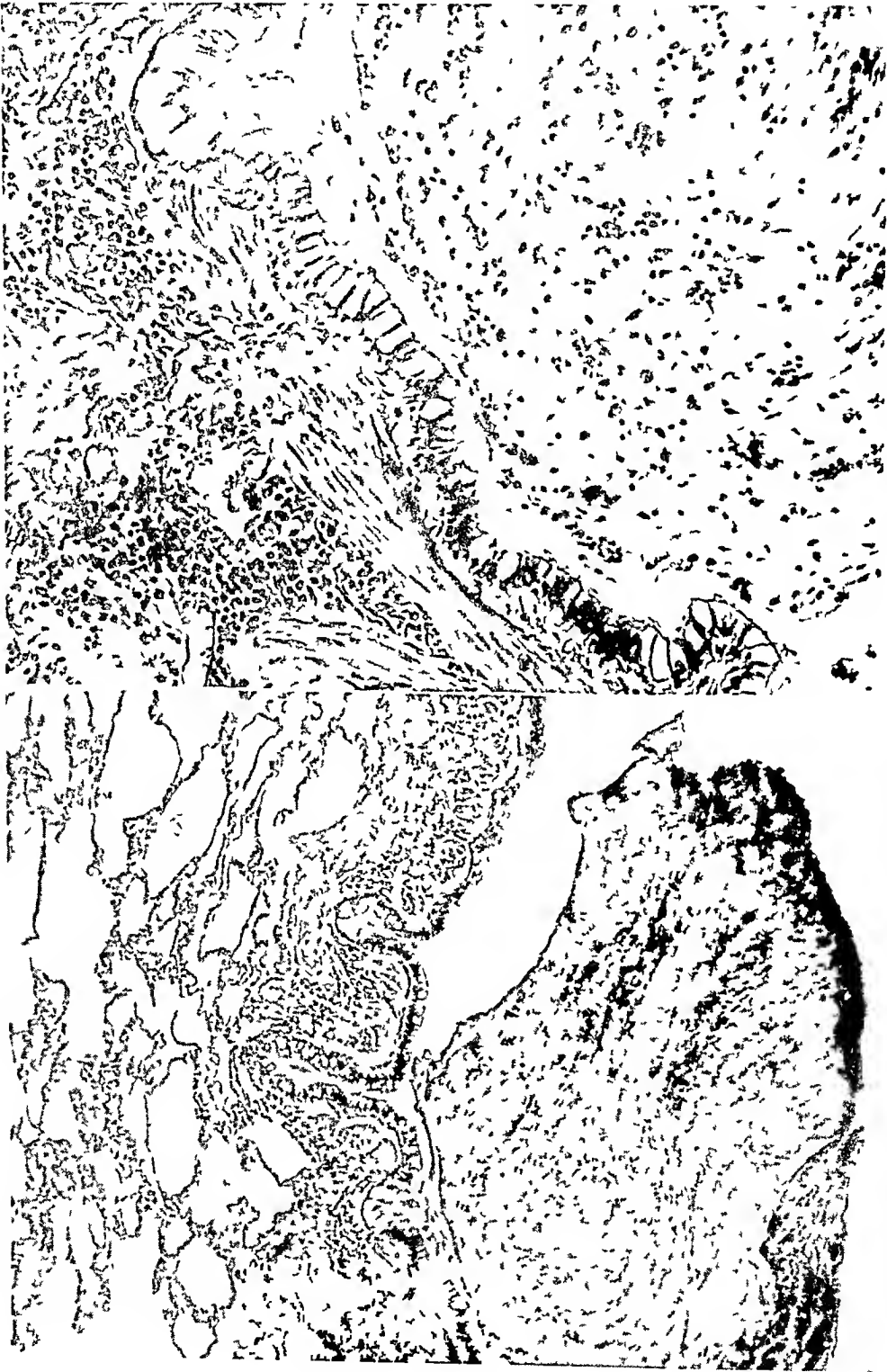


FIG 3 Small bronchus (low power and high power) Mucous plug Prominent goblet cells Slight inflammatory reaction Little change in basement membrane

one case of death after codeine. The symptoms of asthma increased following morphine and the patients died respiratory deaths resembling strangulation. In two autopsied cases the entire bronchial tree was filled with a tenacious mucous exudate. The authors believe that

- 1 Morphine depresses the respiratory center and makes respiration more shallow

- 2 Abolition of the cough reflex makes it more difficult to expel mucous plugs

- 3 Opiates may cause a hive reaction in the bronchial tree

Jackson² states that morphine and other opium derivatives are able to produce bronchospasm by direct action upon the bronchial muscles, independently of the innervation, and that such a spasm is lasting and difficult to relieve by drugs with an opposing action such as epinephrine which stimulates the bronchodilator nerve endings. He raises the question as to the existence of two separate and distinct forms of bronchial asthma, the one of nervous, the other of muscular origin. Feinberg³ considers morphine idiosyncrasy rather frequent among asthmatics and that a fatality may be hastened or brought on by its use. Sollmann⁴ states that therapeutic doses of morphine produce slight bronchial relaxation whereas large doses cause marked constriction. "The relaxation may play a part in the relief of bronchial spasm (asthma), while the constriction may contribute to the asphyxia of toxic doses. The effects are peripheral for they occur on excised bronchial muscle." "The constrictor action is not antagonized by atropine and must, therefore, be on the muscle or myoneural junction." "Unless there is nausea the secretion of mucus appears diminished. This may be explained largely by the suppression of cough, permitting a longer sojourn of the mucus in the bronchi, with consequent removal of its water by absorption and drying, but there may also be a central depression." Personally I consider morphine a dangerous drug in asthma.

Would bronchoscopy have helped this patient? The finding of large amounts of tenacious mucus in the bronchial tubes and the knowledge that this is a common condition in severe asthma suggest that mechanical removal of the exudate would be exceedingly useful. The technical difficulties and possible danger of bronchoscopy in a seriously ill patient must be considered, but in some instances it will probably prove to be a life saving procedure.

Recently the inhalation of helium and oxygen has been suggested for the treatment of severe or intractable asthma. A mixture of oxygen 20 per cent and helium 80 per cent has one-third the density of atmospheric air and appears to enter narrowed air passages with much greater ease. Barach^{5,6} and Maytum et al⁷ have had some very favorable experiences. In severe asthma where the patients had become refractory to epinephrine, the relief of the paroxysm was accompanied by a return to normal epinephrine sensitiveness. With five patients in status asthmaticus Barach believes that lives were saved. Cylinders containing helium and oxygen in proper percentages are now on the market, and the inhalation of this mixture gives promise of being a very useful therapeutic agent, deserving of further clinical trial.

The pathological changes noted in this patient have been described by other observers. Emphysema, large amounts of thick tenacious mucus in the bronchial tree, infolding of the epithelial lining, fibrosis, prominence of goblet cells and

mucous glands, thickening and hyaline degeneration of the basement membrane, infiltration of the tissues with eosinophiles, all are well known findings. Others have described in addition increased thickness of the walls of the bronchi, hypertrophy of the muscle layers, myositis of the bronchial muscles and adhesive pleuritis. Hueber and Koessler⁸ in their classical study of the pathology of bronchial asthma made very careful measurements of the bronchial tubes and came to the conclusion that the actual thickness of the walls of the bronchi and bronchioles of more than 0.2 mm. outside diameter is definitely increased.

Does a combination of the above described tissue changes indicate a characteristic pathology for bronchial asthma? Walzer⁹ has well summarized the position of those who take a negative stand. He states that there is no one significant abnormality present in every case of asthma nor are there any findings not met with in some other respiratory disturbance. He believes that the common secondary bronchitis and emphysema can cause increased thickness of the muscle layer and can produce most of the other changes. On the other hand Michael and Rowe¹⁰ and Alexander¹¹ have stated that a pathological picture characteristic of bronchial asthma does exist. Hueber and Koessler⁸ believed that the simultaneous occurrence of eosinophilia in the blood, sputum, and tissues does not occur in any other condition which could be confused with bronchial asthma.

SUMMARY

A case of status asthmaticus is reported. Death appeared to be due to cardiac and general exhaustion. The role of the administration of large amounts of epinephrine and of morphine is discussed. Bronchoscopy is recommended in selected cases. The inhalation of helium and oxygen is considered. The pathological findings are similar to those reported in other patients who have died in acute asthma.

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EDITORIAL

THE PHYSIOLOGIC SIGNIFICANCE OF SWEATING

Human sweat glands, which according to Klose number about 2,380,000 are distributed over the entire surface of the body. Those in the axillary and inguinal regions are larger and of slightly different construction than are those situated elsewhere. The number in a specific region is greatest in the palms of the hands and the soles of the feet, next greatest in the forehead and least on the trunk and extremities. Kuno has reported that the extremities of Japanese, which are subjected to much exposure, contain a greater number of sweat glands than do the extremities of other races whose extremities are not exposed.

Sweating induced by heating the body occurs as a reflex mediated through the central nervous system and the sympathetic nerve fibers which supply the sweat glands. Langley, who first accurately described the secretory nerve fibers of animals, showed that they were part of the thoracolumbar or sympathetic division of the autonomic nervous system. He demonstrated that sympathetic nerves contained fibers which control vasomotor reactions and sweating. If the vasomotor fibers were completely removed, sweating could not be demonstrated. Later, he showed by operation on cats that the nerve fibers concerned with sweating corresponded to the segmental distribution of the sympathetic nerves in the spinal nerves. He showed further that the area of skin supplied by the gray rami of each ganglion corresponded largely with the area of skin supplied by the homologous posterior root fibers.

Langley's observations on cats are applicable to man, as recent studies following bilateral cervicothoracic ganglionectomy, bilateral lumbar ganglionectomy and bilateral ventral rhizotomy have confirmed this segmental distribution of the sympathetic nerve fibers to the sweat glands. As a result of these studies it is possible to determine by tests of sweating what part of the sympathetic nervous system has been interrupted or removed.

There has been much controversy relative to the centers which control sweating. Evidence has been advanced by various investigators that sweat centers are situated in the cerebral cortex, the hypothalamic regions, the medulla oblongata and the spinal cord.

From a study of lesions of the spinal cord which affected soldiers, Andre-Thomas concluded that spinal centers for the innervation of the sweat glands of the head, neck, upper extremities and upper portion of the thorax, were situated between the eighth cervical and the sixth thoracic segments, and that those for the innervation of the sweat glands of the lower part of the trunk and extremities were situated between the sixth thoracic and upper lumbar segments. Head and Riddoch have shown that sweating which ceases temporarily after removal of the impulses from higher centers by

complete transection of the spinal cord not only returns eventually but that it becomes excessive

Since sweating may be produced by mental effort, Kuno suggested that there might be a cortical center, and in confirmation of this, Guttman reported that sweating occurred in response to electric stimulation of the cerebral cortex. However, Kuntz suggested that sweating induced by stimulation of the cortex might be produced by secondary impulses to the autonomic center in the hypothalamus. Cushing's studies on man have demonstrated that excessive sweating can be produced by injection of solutions of posterior pituitary, or pilocarpine into the cerebral ventricles. Since sweating is a part of the mechanism for reducing body temperature, it is probable that the center which controls it is situated in the hypothalamic region where the center for the regulation of the body temperature apparently is situated.

The most commonly used methods for determining sweating are the starch-iodine method and the cobaltous chloride method. In both of these tests the estimation of the degree of sweating depends on the change in the color of the material applied to the skin. In the starch-iodine test, when the skin is dry, the powder remains white, with the presence of sweat the color of the powder becomes deep blue-black. In the cobaltous chloride method, when the skin is dry the area to which the solution has been applied is deep blue in color but turns red on the appearance of sweat.

• Sweating, which is a normal physiologic response, varies greatly among different individuals and under varying conditions. The reactions of the excretion of sweat are very sensitive to psychogenic factors, as is seen by the response to pain, gastrointestinal cramp, anxiety, joy, and the administration of nicotine. It is said that, in general, obese people, those who eat excessively, and those who have hyperthyroidism sweat excessively. Sweating is also increased in some cases of hemiplegia, herpes zoster, tuberculosis, hyperpituitarism, in most fevers, and in vasomotor disturbances such as Raynaud's disease. However, little clinical significance can be given to the presence of increased perspiration in any of these conditions. An example of marked increase in local sweating is that which affects the extremities without evidence of peripheral vascular disease. In some cases the hyperhidrosis in the hands and feet is so marked that it produces maceration of the skin and is disabling to a large degree. Adson, Craig, and Brown were of the opinion that this condition is a dysfunction of the sympathetic nervous system, which originates in the higher cerebral centers.

Diminution of sweat may occur in cases of poliomyelitis, multiple sclerosis, syringomyelia, myelitis, tumor of the spinal cord, and orthostatic hypotension. Since orthostatic hypotension is a disease which affects the vasomotor nerves and also the fibers that control sweating, the anhidrosis which occurs in orthostatic hypotension is of definite clinical importance. It is one of the characteristic abnormalities of the syndrome. Chew, Allen and Barker have reported anhidrosis to be present in 17 out of 21 cases. This lack of sweating varies in extent of distribution more or less with the

severity of the orthostatic hypotension. Anhidrosis also may occur as a result of degeneration of the sweat glands. Fog reported a case in which it followed a long standing febrile illness and biopsy of skin revealed that only about half of the sweat glands were present while the other half had undergone degeneration. A few cases in which generalized anhidrosis was due to congenital and general developmental anomaly of the skin have been reported.

Following the advent of surgical procedures on the sympathetic nervous system, it was found that anhidrosis produced by the interruption of the sympathetic pathways to a given cutaneous area is permanent. This provided a method for determining the distribution of the sympathetic nerve fibers to the sweat glands. Since hyperhidrosis was presumably the result of dysfunction of the sympathetic nervous system, sympathetic ganglionectomy was performed for the relief of this condition. The first two surgical interruptions of the sympathetic pathways for hyperhidrosis were made in 1921 by Kotzareff and in 1928 by Braeucker. In 1932 and 1934 Adson, Craig and Brown reported six cases of essential hyperhidrosis in which sympathetic ganglionectomy produced permanent relief. White has treated one patient who had hyperhidrosis, by paravertebral injection of alcohol into the upper thoracic ganglions, the sweating was definitely subnormal at the end of a year.

Although a great amount of investigative work has been done and considerable information has been obtained concerning the distribution of the sympathetic fibers to the sweat glands, the situation of sweat centers and the physiology of sweating in man, the clinical use of this knowledge is limited. According to Brown, the response of the secretion of sweat to a high environmental temperature determines the presence or absence of generalized or localized forms of anhidrosis, hypohidrosis or hyperhidrosis, and sweating tests will demonstrate whether complete denervation of the sympathetic fibers to a given area is present after sympathectomy. Repetition of the sweating tests at later intervals determines whether regeneration of nerve fibers has occurred. Clinically, anhidrosis is an important characteristic abnormality of orthostatic hypotension and surgical interruption of the vasomotor pathways will produce permanent relief in cases of hyperhidrosis.

G M R

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REVIEWS

The Comparative Anatomy of the Nervous System of Vertebrates Including Man
By C U ARIENS KAPPERS, M D, the late G CARL HUBER, M D, and ELIZABETH
CAROLINE CROSBY, Ph D 2 volumes, 1845 pages The Macmillan Co, New York
City 1936 Price, \$16 00 per set

The names of the authors of this important work are adequate guarantee of ability to handle an admittedly difficult subject Started over ten years ago as a translation of Kappers' German text on the same subject, it soon outgrew the status of a translation and blossomed as a full fledged new work based upon the combined studies of both the senior and junior authors with such additions from other sources as seemed requisite to cover the broad scope of the work

It may be stated at the outset that this book is not for the general practitioner of medicine or for those not familiar with neuro-anatomical structure and the technique of its investigation and presentation But as a reference work, of which more will be said later, and for those concerned in neuro-anatomy and its application, it is a gold mine of information

The work consists of two volumes of about 850 pages each In spite of its size it is almost literally a glorified abstract of the subject matter covered, rather than an exhaustive discussion of any of the multiple subdivisions into which it divides itself This is necessarily so because of the breadth of the subject itself

The first volume discusses the phylogenetic development of the neurone, the spinal cord, the medulla oblongata in its broad sense, including the pons and the cerebellum The structural significance of the spinal cord of each Class is discussed beginning with Amphioxus and ending with man The same phylogenetic sequence is observed in describing the medulla oblongata, but here the subject is discussed in functional systems which are traced through the various Classes Taste and tactile sensibility are first described, followed by the lateral line and vestibulo-cochlear afferent systems each being carried through the ascending forms of the vertebrate filum The efferent motor system is similarly treated, including those motor centers resident in the midbrain The organization of the reticular formation is then discussed Under this head an unusual definition of the "final common path" is presented with a completely erroneous reference to Sherrington (1906) as the basis of the definition The correlative function of these reticular centers is clearly demonstrated, but their acceptance as a final common pathway in the original sense of Sherrington is much to be doubted An excellent discussion of the cerebellum concludes this volume

Volume II treats of the midbrain and diencephalon as a unit to which about one-fourth of the volume is dedicated The remaining three-fourths is devoted to the telencephalon The analysis of the telencephalon is divided into two parts The first takes up the non-mammalian forms, describing them in serial order up to the mammal The latter is also included in this grouping except for the nonolfactory cortex This subject is reserved for a special chapter in which it is treated in considerable detail The discussion of the fundamental structure of the forebrain as determined by embryological evidence is regrettably lacking in completeness in that it does not include Kingsbury's (1920, 1922) interpretation of this process, particularly so since this author's findings are at variance with those favored in this book, though none-the-less have been widely accepted elsewhere A somewhat similar criticism may be made regarding the otherwise splendid discussion of the cerebral cortex in which the illuminating recent findings from the laboratories of Yale are conspicuous by their absence This is explainable on the basis of the lapse of time since the inception of the work now under review though the omission seems hardly to be justified on this basis

Each chapter of the book contains a resume of the subject matter treated of in the chapter. This is arranged under subtitles indicative of the Classes under consideration and is an important and valuable feature of the book. The chapter ends with a bibliography pertaining to the chapter and arranged under subtitles like that of the resume preceding it. Thus the seekers of bibliography in the lateral line system of Plagiosomes, or a like subject treated of in this book can in a moment locate the object of his search. These subject classification references consume in all about 250 pages and constitute in themselves a justification for the publication of the work.

Woven throughout the text are examples of the thesis of neurobiotaxis so closely associated with the name of the senior author, on the basis of which apparently disharmonious anatomical conditions of different species are harmonized and their significance interpreted.

The seven hundred plus illustrations adequately cover the text but the appearance of many of them is marred by indifferent labeling and the almost complete lack of descriptive technic in the legends limits their intelligent interpretation to those who are completely familiar with neuro-histological technic. This is a pity. A compensation exists, however, in the profusion of illustrations which the authors and publisher have managed to crowd into this work and still hold its publishing price at an astonishingly low figure. This is something for which an appreciative public will undoubtedly give thanks.

These volumes fill a want which has long existed in the English language and will remain as a worthy monument to the industry and genius of those who have produced them, one of whom, Dr G. Carl Huber, unfortunately did not live to witness this climax to a busy and fruitful career.

C L D

Recent Advances in Diseases of Children By WILFRED J. PEARSON, D.S.O., M.C., D.M., F.R.C.P., and W. G. WYLLIE, M.D., F.R.C.P. 566 pages, 14.5 × 20.5 cm. Third Edition. P. Blakiston's Son and Co. Inc., Philadelphia, Pennsylvania. 1935. Price, \$5.00.

The title "*Recent Advances in Diseases of Children*" does not correctly state the subject matter of this edition. In reality an attempt has been made to offer the general practitioner brief accounts of the illnesses of the young in a manner in which they are met in every day practice. The authors are concerned with the subjects primarily from a clinical aspect, important scientific data are mentioned if they are an aid clinically.

Certainly one of the assets of this book is its excellent organization which will make it helpful to the general practitioner. One is also impressed, however, by the lack of scientific discussion and of adequate references.

W M S

The Principles of Bacteriology and Immunology By W. W. C. TOPLEY, M.A., M.Sc., F.R.C.P., F.R.S., Professor of Bacteriology and Immunology, University of London, and G. S. WILSON, M.D., F.R.C.P., D.P.H., Professor of Bacteriology as Applied to Hygiene, University of London. London School of Hygiene and Tropical Medicine. Second Edition. 1645 pages, 18.5 × 25 cm. William Wood and Co., Baltimore. 1936. Price, \$12.00.

The years that have passed since the publication of the first edition of this book have been years of renewed activity in research in the field of bacteriology and immunology. This has made necessary no inconsiderable revision of the text. A number of chapters have been rewritten, many have had much new material added, and hardly one has been left without partial revision. Several new chapters have been

included. All of this has been accomplished without greatly enlarging the book by a discreet omission of some of the older work and by a judicious selection from the newer. Nevertheless, its publication in a single volume in response to former criticisms would seem to make for inconvenience in reading. The second edition will undoubtedly maintain the same position as the first in the forefront of texts on the subject.

F W H

Chemical Procedures for Clinical Laboratories. By MARJORIE R. MATTIC, A.B., Sc.M. 520 pages, 16×24 cm. Lea and Febiger, Philadelphia, Pa. 1936. Price, \$6.50.

This is a comprehensive manual for chemical clinical laboratories. The author has included methods for the determination of the various constituents of blood, urine, feces, cerebro-spinal fluid and other body fluids. The chapter dealing with the chemical treatment of transudates and exudates is to be commended. The book should be valuable to those laboratories inexperienced in extensive work of this nature for the author has incorporated precautions and helpful changes in many determinations and has included only those methods which she has found satisfactory in her own laboratory. In other laboratories the book will be acceptable only in part since many of these methods will be neither suitable nor sufficiently recent for their use.

E M R

Cancer Committee Studies. California Medical Association. 123 pages. J. W. Stacey, Inc., San Francisco, California. 1936. Price, \$7.50.

The book is paper bound and of small portfolio, with 123 pages. It contains the report of a cancer commission created by the House of Delegates of the California Medical Association in 1931. This commission appointed sub-committees to report on all phases of cancer therapy and in all specialties. The book is a timely one and should be read by every person interested in the cancer problem.

The first chapter is on Radiology. The Radiological Committee treats the question of "Radiology in the Treatment of Cancer," in a very safe and conservative manner. Following this, each special subject is reported upon by its own committee.

The great value of this book lies in the fact that it is not based on the experience of one man, nor one institution. "The Commission has made what it believes to be the first organized attempt to set forth the opinion of the medical profession rather than that of any one individual or clinic, or even one specialty." The purpose of the study is "to develop a better agreement in the profession and a wider diffusion of knowledge of the diagnosis and adequate treatment of early cancer." This aim has been closely adhered to and the book contains much valuable knowledge carefully compiled. The most up-to-date opinions about symptoms, onset, methods of diagnosis, treatment of early cancer, etc., are set forth, and where there is a controversy of opinion, especially as to treatment, both methods are given and the reasons for them stated. This book is a valuable adjunct to any physician's library.

G E W

COLLEGE NEWS NOTES

GIFTS TO THE COLLEGE LIBRARY

Grateful acknowledgment is made of the receipt of the following donations to the College Library of publications by members

Books

- Dr Russell L Cecil, Fellow, New York, N Y, "Diagnosis and Treatment of Arthritis",
- Dr Henry A Christian, Fellow, Boston, Mass, two autographed books, "The Diagnosis and Treatment of Diseases of the Heart" and "Medical Papers," the latter being a volume containing contributions dedicated to Dr Christian
- Dr E B Krumbhaar, Fellow, Philadelphia, Pa, an autographed copy, "Clio Medica XIX Pathology",
- Dr Edward C Mason, Fellow, Oklahoma City, Okla, an autographed book "Why We Do It",
- Dr William D Nimelh, Fellow, Mexico City, D F, a book of poems by Dr Nimelh

Reprints

- Dr Dean B Cole, Fellow, Richmond, Va, three reprints—"The Treatment of Pulmonary Tuberculosis" (with Walter L Nalls, M D), "Ambulatory Pneumothorax" (with Edgar C Harper M D), "Therapeutic Use of Iodized Oil in Pulmonary Disease" (with Edgar C Harper, M D),
- Dr Lewis B Flinn, Fellow, Wilmington, Del, one reprint—"Preliminary Observations on the Clinical Use of Zinc-Protamine-Insulin in Out-Patients",
- Dr Cecil M Jack, Fellow, Decatur, Ill, one reprint—"Some Unusual Features of Lung Cancer",
- Dr Hubert C King, Fellow, Lakewood, Ohio, one reprint—"Prognosis in Coronary Heart Disease and After Coronary Occlusion",
- Dr Sinclair Luton, Fellow, St Louis, Mo, one reprint—"Clinical Use of Digitalis Variables Encountered",
- Dr Theodore H Morrison, Fellow, Baltimore, Md, one reprint—"Idiopathic Ulcerative Colitis with a Report of an Unusual Case",
- Dr Albert E Russell, Fellow, Washington, D C, one copy of the Second Annual Memorial Lecture, "Silicosis and Other Dust Diseases",
- Dr Louis J Bailey, Associate, Detroit, Mich, one reprint—"Paralysis of the Third Cranial Nerve Due to Spontaneous Hemorrhage Within the Nerve in the Latter's Intracranial Course" (with E S Gurdjian, M D),
- Dr Samuel Morrison, Associate, Baltimore, Md, six reprints—"The Pharmacopeia and the Physician" (with Julius Friedenwald, M D), "The Treatment of a Lung Abscess Due to *Bacillus Coli* with a Lytic Filtrate" (with Raymond E Gardner, Sc D), "The Elimination of Various Dyes From the Pavlov Pouch of Dogs" (with David L Reeves, M D and Raymond E Gardner, Sc D), "The History of the Development of the Stomach Tube With Some Notes on the Duodenal Tube" (with Julius Friedenwald, M D), "The Medical Treatment of Peptic Ulcer" (with Julius Friedenwald, M D), "Value, Indications, Limitations and Technic of Colonic Irrigation" (with Julius Friedenwald, M D),
- Dr William Kendrick Purks Associate, Vicksburg, Miss, seven copies of reprint—"Total Thyroidectomy for Heart Disease",

Dr William R Wirth, Associate, New Orleans La, one reprint—"The Significance of Cardiac Arrhythmias as Encountered in General Practice"

Miscellaneous

- Dr Robert E Schlueter, Fellow, St Louis, Mo, a photograph album containing photographs of the pilgrimage to William Beaumont's grave by the American College of Physicians during its 1937 Session in St Louis,
 Dr John A Shuman, Fellow, Los Angeles Calif, two lectures on "Southern California Medicine, Indian to Spanish Inclusive",
 Rev Harvey K Heebner, Editor, The Schwenkfeldian, Philadelphia Pa a copy of "A Memorial to Dr James M Anderson" (Master),
 Mr M R Kneiff, Executive Secretary, Catholic Hospital Association, St Louis, Mo, one copy, "Special Directory Number of *Hospital Progress*"

At the last annual meeting of the State Medical Association of West Virginia, the following members of the College were elected to office Dr Charles W Waddell (Fellow), Fairmont, W Va, President, Dr Arthur A Shawkey (Fellow), Charleston, W Va, Second Vice President, Dr T M Barber (Associate), Charleston, W Va, Treasurer

Commander Eben E Smith (Fellow), Medical Corps, United States Navy, has relieved Commander Louis H Roddis (Fellow), Medical Corps, United States Navy as editor of the "United States Naval Medical Bulletin" and as secretary of the Postgraduate Board

During the Centennial Celebration, Davidson College, on June 8, conferred the honorary degree of Doctor of Science on Lieutenant Colonel James Stevens Simmons, Medical Corps, United States Army, now stationed at the Army Base, Boston Mass, in recognition of his investigations on tropical diseases and preventive medicine

At the eighty-seventh annual meeting of the Illinois State Medical Society, held in Peoria, May 18-20, Dr Samuel E Muson (Fellow and Governor for southern Illinois) was elected President-Elect of the Society

Dr Louis F Bishop, Jr (Fellow), New York, N Y, recently attended, as a guest speaker, the West Virginia State Medical Association meeting in Clarksburg. He addressed the West Virginia Heart Association, May 24, on "Bundle Branch Block", the Section on Internal Medicine, May 24, on "Fugitive Arrhythmias", and the General Assembly, May 25, on "Prevention of Heart Disease"

Dr Frank Burge (Fellow), Philadelphia, Pa, has been appointed Editor-in-Chief of "Diseases of the Chest," official journal of the American College of Chest Physicians. Dr Burge is also an Associate Editor of Chest Diseases of the Cyclopedia of Medicine

The American College of Chest Physicians is the new name adopted by the Federation of American Sanitaria, the change in name being adopted at Atlantic City during June

Dr Sinclair Luton (Fellow), St Louis, Mo, presented a scientific exhibit on "Major Errors Involved in the Use of Droppers for Liquid Digitalis Preparations" at the eightieth annual meeting of the Missouri State Medical Association during May

Dr Roy S Leadingham (Fellow), Atlanta Ga, presented a scientific exhibit and paper on "Rat Bite Fever" at the meeting of the American Society of Clinical Pathologists in Philadelphia, June 2-5

The Fifth International Congress of Radiology will convene at the Palmer House, Chicago, September 13-17, 1937. It will be the first time that the world leaders in the medical and scientific development field of roentgen-ray and radium have met in America. The American Roentgen Society, the American College of Radiology, the Radiological Society of North America, and the American Radium Society will merge their meetings with the International Congress. "The Unity of Medicine" will be the theme of the entire Congress. Leaders in other branches of medicine will participate. More than 250 scientific papers will be read. They will be delivered in each lecturer's own language, but will be flashed on screens in English, German and French, as the papers are read.

The General Secretary of the Congress, Dr Benjamin H Orndoff (Fellow), is in charge of the headquarters at 2561 North Clark Street, Chicago. Dr George E Pfahler (Fellow), Philadelphia, is one of the honorary vice-presidents.

Dr Nathan B Van Etten (Fellow), New York, N Y, Speaker of the House of Delegates of the American Medical Association, addressed the general assembly of the Minnesota State Medical Association at St Paul May 4, on 'Medical Care for All Americans'.

At the fifteenth annual meeting of the Philadelphia Heart Association, Dr William D Stroud (Fellow) was reelected President, Dr David Riesman (Fellow) was elected Vice President, Dr Thomas M McMillan (Fellow) was elected Secretary, and Dr Edward B Krumbhaar (Fellow) was elected a member of the Board of Governors.

Dr William E Robertson (Fellow) was inducted as President of the Philadelphia County Medical Society on July 1. Dr Louis H Clerf (Fellow) has been elected a Director.

Dr E J G Beardsley (Fellow) Philadelphia, Pa, was elected Secretary-Treasurer of the American Association of the History of Medicine at the last annual meeting of that organization at Atlantic City during May.

Dr David Riesman (Fellow) received the honorary degree of Doctor of Laws from the University of Wisconsin at commencement June 21, 1937.

At the 131st Annual Meeting of the Medical Society of the State of New York, held at Rochester, N Y, May 24, 25, 26, 1937, Dr William A Groat (Fellow), Syracuse, N Y was elected President-Elect of the Society.

Dr Dwight O'Hara (Fellow), Professor of Preventive Medicine in Tufts College Medical School, has been appointed to the newly created position of vice-dean, to supervise clinical instruction in the third and fourth years.

Dr Alfred Friedlander (Fellow), Professor of Medicine and Dean at the University of Cincinnati College of Medicine, has been appointed superintendent of the General Hospital to fill the vacancy caused by the death of Dr Henry H Langdon. Dr Friedlander will continue his work in the medical school and act as superintendent only until a successor for the latter position can be found.

The American Association for the Study and Control of Rheumatic Diseases held its fourth annual meeting at Atlantic City under the presidency of Dr Russell L Cecil (Fellow), New York City. Dr Cecil presented a paper on "The Necessity of Certain Criterion for the Diagnosis and Cure of Rheumatic Arthritis", Dr Bernard L Wyatt (Fellow), Tucson, Ariz, gave a paper on "Experimentally Induced Jaundice", Dr Philip S Hench (Fellow) Rochester, Minn, gave a paper on "Further Observations of the Effect of Jaundice on Atropic Arthritis and Fibrositis"

Dr Lewellys F Barker (Fellow), Baltimore, Md, discussed the "Progress of Endocrinology" at the twenty-first annual meeting of the Association for the Study of Internal Secretions at Atlantic City in June, under the presidency of Dr F M Pottenger (Fellow), Los Angeles

Dr Paul D White (Fellow), Boston, Mass, delivered the Alvarez Lecture on "The Differential Diagnosis of Cardiac and Gastro-Intestinal Disorders," before the fortieth annual meeting of the American Gastro-Enterological Association at Atlantic City in June, under the presidency of Dr Chester M Jones (Fellow), Boston, Mass

Dr Lewis A Conner (Fellow) New York City, delivered the annual Henry Jackson Lecture of the New England Heart Association, April 30, on certain aspects of rheumatic fever and rheumatic heart disease

Dr Walter M Boothby (Fellow), and Dr William A Plummer (Fellow), Rochester, Minn, addressed the annual meeting of the American Association for the Study of Goiter, held in Detroit, June 14-16, on "Interpretation of Basal Metabolic Rates in the Relatively Normal Individual"

Dr George A Harrop (Fellow), Baltimore, Md, has been appointed Director of Research on the staff of E R Squibb & Sons, according to a recent announcement. Dr Harrop has been Assistant Professor of Medicine at Johns Hopkins University School of Medicine. E R Squibb & Sons are constructing a new research laboratory at New Brunswick, N J. "Investigation along scientific lines will be carried on without necessary regard to its immediate practical outcome. It is also planned to undertake active clinical investigation with which to supplement and give orientation to the laboratory studies"

Dr Horace W Soper (Fellow), Dr Frank D Gotham (Fellow), and Dr Lee Pettit Gay (Fellow), have been elected President, Vice President and Treasurer, respectively, of the recently formed Missouri Chapter of the National Society for the Advancement of Gastro-Enterology

The following Fellows were selected to present graduate lectures in connection with the twenty-first annual course of medical lectures and clinics of the University of Washington from July 19-23. Dr Anton J Carlson, Professor of Physiology, University of Chicago, Dr William S Middleton, Professor of Medicine, University of Wisconsin Medical School, Madison, Dr Hans Lissei, Clinical Professor of Medicine, University of California Medical School, San Francisco

Dr Mary Riggs Noble (Fellow), Philadelphia, Pa, was elected Treasurer of the American Medical Women's Association at its meeting in Atlantic City in June

Dr Jay A Myers (Fellow), Minneapolis, Minn, was elected President of the National Tuberculosis Association at its annual meeting, June 2

Dr Ross M Chapman (Fellow), Towson, Md, was installed as President of the American Psychiatric Association at its annual meeting in May

Dr Hugh B Campbell (Fellow), Norwich, Conn, has been elected President-Elect of the Connecticut State Medical Association Dr Charles F Turkington (Fellow), Litchfield, is President during the present year

Dr William R Brooks (Fellow), Fort Smith, Ark, has been elected Secretary of the Arkansas State Medical Association for the coming year

OBITUARIES

DR JOHN WYCKOFF

The sudden death of Dr Wyckoff (Fellow) on June 1, 1937, at the age of 55 years, removed from this scene, in the prime of life and at the height of his professional career, one of the most widely beloved and respected members of the profession in New York City

Born in Tindivanam, India, of Dutch Reform American Missionary parents, he spent two years in undergraduate study at Rutgers College, which institution later (1920) conferred upon him an honorary M A degree and still later made him a Trustee

He was graduated in 1907 from the New York University and Bellevue Hospital Medical College and served his internship in Bellevue Hospital After spending some time in various clinics in Germany he returned to New York to take up the practice of internal medicine In 1914 he was married to Miss Elizabeth Crane Porter of Claverock, New York, who with his three children survives him

Almost immediately after his return from study abroad he was made an Instructor in Medicine in the New York University school, in which he rose successively to the ranks of Clinical Professor, Associate Professor and finally (1932) Professor of Medicine To his responsibilities as head of the department of medicine were added about the same time the onerous duties of Dean of the School

He served successively as Adjunct Assistant Physician, Assistant Physician, and Physician and Director of the Third Medical Division of Bellevue Hospital, in which institution much of his professional life was spent

One of the very first of the efforts directed toward the special care and rehabilitation of heart patients was the Bellevue out-patient cardiac clinic, established in 1911 by Dr Hubert V Guile Two or three years later Dr Wyckoff became associated with Dr Guile in this clinic and, upon the

retirement of the latter in 1919, was made its head. Under his skillful guidance the clinic became one of the important agencies of the city for the training of physicians in heart diseases.

The special interest of Dr. Wyckoff in diseases of the heart was expressed in many ways. His writings were chiefly upon different aspects of this subject. For a long time he served as Chairman of the Heart Committee of the New York Tuberculosis and Health Association and of the Association of Cardiac Clinics. He was a Director, and later President, of the American Heart Association. In all of these capacities his work was characterized by the same unusual degree of energy, enthusiasm, vision and judgment that marked his services to the medical school and that played so important a part in the rapid development of that school. Indeed, it is given to few men to show such a record of successful achievement in so many fields of medicine as John Wyckoff could show.

His memberships included those in the New York County and State Medical Societies, American Medical Association, New York Academy of Medicine (Trustee, 1936), Association of American Physicians, American College of Physicians, Interurban Clinical Club, American Clinical and Climatological Association, American Association for the Advancement of Science, Association of American Medical Colleges (President, 1936).

But the mere listing of his accomplishments, appointments and connections would give a sadly inadequate picture of John Wyckoff the man. The things which won for him the deep affection and admiration of his fellow physicians and many friends were not so much his brilliant accomplishments as the personal qualities of modesty, honesty, courtesy, fair-mindedness and consideration for others. The world is much the poorer for the passing of John Wyckoff.

The above information has been supplied by Dr. Lewis A. Conner, F.A.C.P.

C. F. TENNEY, M.D.,
Governor for Eastern New York, New York

DR. DOUGLAS BROWN

Dr. Douglas Brown (Fellow), Veterans' Administration Facility, Castle Point, N. Y., died June 6, 1937, at the age of sixty-seven.

Dr. Brown was born in New York City, later removing to Pottstown, Pa., where he attended the public schools. He attended the Sheffield Scientific School of Yale University, later entering Columbia University College of Physicians and Surgeons and graduating with the M.D. degree in 1894. In his early experience he was House Physician to the Fourth Division of the Bellevue Hospital, and Clinical Assistant in Neurology at the Vanderbilt Clinic, both of New York City. During 1908 and 1909 he served under General Gorgas at the Ancon Hospital, Panama. In 1910 he took post-graduate work at the Allgemeines Krankenhaus, Vienna, in Pathology, Bac-

teriology, Internal Medicine, and Diagnosis. He entered the U. S. Veterans' Administration and served on various assignments over the United States being classed as Internist-Expert in the Veterans' Administration.

Dr. Brown made numerous contributions to the literature. He was a member of the New York County Medical Society, the Medical Society of the State of New York, the American Medical Association, the Association of Military Surgeons, the Medical Veterans of the World War, the American Public Health Association, and had been a Fellow of the American College of Physicians since 1924.

DR. HAROLD BUNCE MYERS

Dr. Harold Bunce Myers (Fellow) of Portland, Oregon, died March 16, 1937, aged 50 years, of coronary thrombosis. At the time of his death he was Professor of Pharmacology and assistant dean of the Medical Department of the University of Oregon, having held both positions for more than 20 years. He took his bachelor's degree in the University of Wisconsin and graduated in medicine at Western Reserve University in 1911. He practiced a short time in Wisconsin and then went to New York where he was a member of the faculty at Bellevue Medical College, coming to Oregon in 1915 as head of the department of Pharmacology.

He had a keen interest in the welfare of medical students, and through contact with all applicants for admission to the school, had a closer acquaintance with the student body than others of the faculty. In many instances students received material aid through anonymous sources, because of his efforts. His activities in the university were many and his counsel was much appreciated.

His scientific contributions were numerous and research work in his department was wisely guided by him. He was a member of many scientific societies.

T. HOMER COFFEN, M.D., F.A.C.P.,
Governor for Oregon

DR. JOHN OSCAR ELROD

Dr. John Oscar Elrod (Fellow), Forsyth, Georgia, aged 59, died in a private hospital in Macon, Ga., on April 21, 1937. He was a native of Adairsville, Bartow County, and had practiced medicine in Monroe County and the adjoining counties for thirty-seven years. He attended the North Georgia Agricultural College and later graduated from the Atlanta College of Physicians and Surgeons, Atlanta (now Emory University School of Medicine), in 1901. He did post-graduate work in medicine and pediatrics at the New York Postgraduate Medical School in 1903.

Dr. Elrod served as major in the Medical Corps of the Georgia National Guard. He served on various committee assignments and in offices of the Medical Association of Georgia, being its president in 1924-25. For

a number of years and until the time of his death, he was a member of the State Board of Medical Examiners. Dr. Elrod was a member of the Monroe County Medical Society, Southern Medical Association, American College of Physicians and the American Medical Association. He was one of the most aggressive and loyal friends of organized medicine, also to his professional, civic and religious duties. Surviving him are his widow, two daughters, Mrs. Carlton Mobley, Atlanta, Miss Mildred Elrod, Forsyth, a brother, G. D. Elrod, Atlanta, his mother, Mrs. G. B. Elrod, Adairsville.

GLLENVILLE GIDDINGS, M.D., F.A.C.P.,
Governor for Georgia

DR. DANIEL FRANCIS DALEY

Dr. Daniel Francis Daley (Fellow), Kingston, Pa., who had been in failing health for many months, died on April 24, 1937. He was born July 16, 1887, in Monmouthshire, Wales. His parents immigrated to this country when the future physician was an infant and his boyhood was spent in Luzerne, Pa., where he attended St. Mary's Academy. At an early age young Daley began to work in and about the coal mines and later through industry, loyalty and persistence in self-education, he was advanced to the responsible position of Chief Clerk of the Temple Coal Company.

Many youths would have considered that the far too early ending of formal education would prove a grievous handicap, but this lack acted as a stimulus in Daniel Daley's life and, without neglecting his duties to his employers, he established and carried out an admirable system of self-education at home. He completed a course of study far more extensive and intensive than many colleges require of their students and, having selected the profession of medicine as a career, he was accepted for entrance in the Jefferson Medical College of Philadelphia where he, in 1915, received his M.D. degree.

Dr. Daley served his internship in the Mercy Hospital, Wilkes-Barre, Pa., in which institution he later was to become pathologist.

Dr. Daley was an indefatigable student. He pursued his studies in the clinics of this country and abroad.

He was a member of the Philadelphia Pathological Society, the American Society of Clinical Pathologists and became a Fellow of the American College of Physicians in 1928.

Dr. Daley was a "good doctor." He was respected by fellow physicians and loved by his patients.

E. J. G. BEARDSLEY, M.D., F.A.C.P.,
Governor for eastern Pennsylvania

DR. EUGENE F. McCAMPBELL

Dr. Eugene F. McCampbell (Fellow), Columbus, Ohio, died May 8, 1937, of pneumonia at the age of fifty-five. Dr. McCampbell was born at

Marysville, Ohio, in 1883. He received the degree of Bachelor of Science in 1906 and the degree of Doctor of Philosophy in 1911 from the University of Chicago. His medical training was received at Rush Medical College, from which he graduated in 1912.

Dr McCampbell was a teacher for a number of years previous to the time he studied medicine. He was Instructor in Bacteriology at the Ohio Medical University from 1903 to 1904, Assistant in Pathology at the University of Wisconsin during 1905 and 1906, Instructor in Bacteriology, 1906-08, Associate Professor of Bacteriology, 1908-10, Ohio State University College of Medicine. He served as Professor of Bacteriology, 1910-13, Professor of Preventive Medicine, 1913-27 and Dean, 1916-27, of the Ohio State University College of Medicine. He was Assistant in Pathology at the University of Chicago during the summers of 1908-11, Secretary and Executive Officer of the Ohio State Board of Health, 1912-16, Pathologist to the Columbus State Hospital, 1909-11. He had been a President of the Columbus Academy of Medicine and also a member of the Ohio State Medical Association, the American Medical Association, and had been a Fellow of the American College of Physicians since 1926. At the time of his death, he was a member of the Staffs of the Mount Carmel, Giant and White Cross Hospitals.

Dr McCampbell was the author of a number of publications, including "Laboratory Methods for Study of Immunity" and co-author of "General Bacteriology."

DR EARL B SWEET

Dr Earl B Sweet, Fellow, died May 22, 1937, in Los Angeles following an operation on May 19. Dr Sweet was born May 4, 1875, in Sloan, Iowa. He came to Los Angeles in 1887 and had his general education in the Los Angeles City Schools. He received his medical education at the University of Pennsylvania from which he was graduated in 1898. Dr Sweet returned to Los Angeles to practise, early limiting his work to that division of effort which comes under Internal Medicine. He was a fine upstanding man, well known to his colleagues and with a wide and friendly acquaintanceship in the community. He was a charter member of the University Club. He belonged to his County, State and the American Medical Associations and the Southern California Medical Association. Though those who knew him realized that he was failing during the last few months, his cheeriness and hope remained with him until the last two weeks when he realized what he had to meet. In his death the community and the profession lost a fine man and member, they send their sympathy to his widow, who survives him.

EGERTON L. CRISPIN, M D , F A C P ,

Regent

MINUTES OF THE BOARD OF REGENTS

ST LOUIS, MO

April 18, 1937

A regular meeting of the Board of Regents was held at the Jefferson Hotel, St. Louis, April 18, 1937, with Dr. Ernest B. Bradley, President, presiding, Mr. E. R. Loveland acting as secretary, and with the following Regents present:

Ernest B. Bradley, *President*,
James H. Means, *President-Elect*,
O. H. Perry Pepper, *First Vice-President*,
David P. Barr, *Second Vice-President*,
Walter L. Biering, *Third Vice-President*,
William Gerry Morgan, *Secretary-General*,
William D. Stroud, *Treasurer*,
William J. Kerr,
Roger I. Lee,
Sydney R. Miller,
George Morris Piersol,
G. Gill Richards,
Robert A. Cooke,
James B. Herrick,
Hugh J. Morgan,
James E. Paulin,
Egerton L. Crispin,
James Alex. Miller,
Francis M. Pottenger,
Charles H. Cocke,
Maurice C. Pineoffs,

and with Dr. Alfred Stengel as acting chairman of the Committee on Constitution and By-Laws.

Abstracted Minutes of the preceding meeting of the Board of Regents were read by the Executive Secretary, and, on motion, approved and read.

President Bradley announced that he had appointed a Committee to confer with the American College of Surgeons, his Committee consisting of the President, President-Elect and First Vice-President.

The Executive Secretary then read communications from Dr. E. W. Gehring, Governor of the College for Maine, dealing with the future policy of the College with respect to requirements of admission and the certification of physicians by the American Board of Internal Medicine, a communication from Dr. H. B. Logie, Executive Secretary of the National Conference on Nomenclature of Disease, thanking the College for its contribution to that organization's work, and a communication from Dr. James D. Bruce, Regent, expressing the opinion that the American College of Physicians should continue to admit to its membership those practicing specialties affiliated with Internal Medicine and also expressing doubt as to the advisability, at the present time, of making certification by the American Board of Internal Medicine a prerequisite to membership.

President Bradley read a communication from Surgeon General Reynolds of the U. S. Army and a reply by Dr. James Alex. Miller, concerning the Harlow Brooks' memorial. Dr. Miller explained that a fund is being raised to be used by a committee in the memory of Dr. Brooks for the cause of medical education. He recommended that if the idea of co-operating appeals to the College either approving the plan, or making a contribution, a general resolution to that effect could be adopted.

On motion by Dr Roger I Lee, seconded by Dr James E Paulin, and regularly adopted, it was

RESOLVED, that the Board of Regents appoint Dr James Alex Miller, a committee of one, to investigate the Harlow Brooks' Memorial Fund, and to report at some subsequent time to the Board of Regents for the appropriate action

In subsequent discussion, it was pointed out that the College is much interested in the project, but not prepared to make a contribution to the Fund

Dr William Gerry Morgan, Secretary-General, was called upon for his report. He reported the deaths of the following members since the last meeting of the Board of Regents

Master

Smithies, Frank	Chicago, Ill	February 9, 1937
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Fellows

Bartley, Elias H	Brooklyn, N Y	January 12, 1937
Busby, James Leslie	Pasadena, Calif	February 18, 1937
Crane, Augustus Warren	Kalamazoo, Mich	February 20, 1937
Fales, Louis Henry	Livermore, Calif	February 13, 1937
Fraser, Benjamin H	Lexington, Ky	March 5, 1937
Ghrist, David Garrison	Los Angeles, Calif	February 3, 1937
Hodges, J Allison	Richmond, Va	December 15, 1936
Johnston, Collins H	Grand Rapids, Mich	December 29, 1936
Laubaugh, Ernest E	Boise, Idaho	December 13, 1936
McKelvy, James P	Pittsburgh, Pa	January 28, 1937
Mink, Owen J	M C, U S Navy	October 21, 1936
Niemeyer, Charles Vincent	Union City, N J	January 11, 1937
Nisbet, Walter Olin	Charlotte, N C	January 18, 1937
Plummer, Henry S	Rochester, Minn	December 15, 1936
Redfern, Thomas C	Winston-Salem, N C	October 16, 1936
Rich, William Lafayette	Salt Lake City, Utah	November 17, 1936
Stearns, William G	Winnetka, Ill	January 11, 1937
Waples, Frank A	Houston, Tex	March 3, 1937
Warren, Luther Fiske	Brooklyn, N Y	January 18, 1937
Wegge, William F	Milwaukee, Wis	November 20, 1936
White, William A	Washington, D C	March 7, 1937

Associate

McCalla, Randolph L	Boise, Idaho	October 10, 1936
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Dr Morgan further reported the following additional Life Members since the last meeting

William Eugene Kendall	Oak Park, Ill
Manfred Kraemer	Newark, N J
James W Hunter, Jr	Norfolk, Va
Herbert B Smith	Corning, N Y
Fresenius Van Nuys	Weston, Mass
George M Settle	Baltimore, Md
Edward B Vedder	Washington, D C
Robert A Peers	Colfax, Calif
Joseph D Condit	Pasadena, Calif
Charles W Stone	Cleveland, Ohio
Samuel A Vogel	Buffalo, N Y
Mills Sturtevant	New York, N Y
Russell M Wilder	Rochester, Minn
Cornelius Oliver Bailey	Los Angeles, Calif

At this point, President Bradley called for resolutions on the deaths of certain of our former Officers and members. Resolutions had been presented both by Dr Robert A Cooke and Dr James Alex Miller on the late Dr Luther Fiske Warren. Dr Cooke presented the following resolution:

LUTHER FISKE WARREN

"The American College of Physicians records the death of Dr Luther Fiske Warren on January 18, 1937, with sorrow and regret.

"Dr Warren became a Fellow of this College in 1919, was chosen one of its Governors in 1931, and served as Regent from 1933 until his death. He was actively interested in the work of the College and served on several committees, especially the important Committee on Credentials.

"Dr Warren prepared for his professional career at the University of Michigan, where he received his medical degree in 1909. His talent for teaching was recognized at once, and he served the Department of Medicine at Michigan until 1912, when he was invited to come to the Long Island Medical College, where he rose rapidly to become Professor of Internal Medicine, which position he filled with distinction from 1917 until his death.

"In addition to his work as a teacher, he filled an important place on the staff of many of the hospitals of Brooklyn and Long Island, and he brought wise counsel, clear vision and sound judgment to his many spheres of activity, and he was an outstanding influence in his community.

"A great understanding, kindly sympathy and complete devotion to the highest ideals of his profession commanded the affection and respect of those in this College with whom he came in contact, and in his death we have lost an honored colleague and a beloved friend. Therefore, be it

"RESOLVED, that the American College of Physicians records its sincerest and deepest sorrow in Dr Luther Fiske Warren's death, its appreciation of his noteworthy services to his community and his profession, and, as a token of the esteem in which his memory will be held by the College, it is directed that this memorial be made a permanent record in the archives of the American College of Physicians and that a copy be sent to the members of Dr Warren's family."

—ROBERT A COOKE, M D, F A C P

Dr James Alex Miller presented the following resolution:

LUTHER FISKE WARREN

"Dr Luther Fiske Warren died at his home, 81 Pierrepont Street, Brooklyn, N Y, on January 18, 1937. Long the head of the Medical Department in the old Long Island College Hospital and after its recharter in 1930 in the Long Island College of Medicine, Dr Warren made his influence felt far beyond the confines of that institution.

"He was born in 1885 in Waterford, Mich. Working his way through school and college, he received his degree in Arts from the University of Michigan in 1907 and his M D from the same institution in 1909, attaining to membership in two honorary societies, Sigma Xi and Alpha Omega Alpha. For three years after graduation he remained at his Alma Mater serving as instructor in Clinical Microscopy and in Medicine.

"In 1912 he was called to Long Island as Assistant Professor of Medicine, being promoted to Associate Professor in 1915, and taking the Chair in Medicine in 1917, for a year as Acting Professor, and as full Professor in 1918. Besides directing the Medical Department of the College Hospital, Dr Warren was Physician-in-Chief at St Johns Hospital and Medical Director of the Brooklyn Home for Consumptives. He was Consulting Physician to the Lutheran, the Coney Island, the Methodist Episcopal Hospitals and the South Side Hospital at Bayshore.

"Dr Warren was a brilliant clinician and teacher, and was endowed with vision and drive to an unusual degree. Among his many extramural activities should be listed the

Presidency of the Kings County Medical Society in 1930, Chairmanship of the Public Health Committee of the Brooklyn Chamber of Commerce, Directorship in the same organization, Directorship of the Brooklyn Council for Social Planning, and Chairmanship of the Brooklyn Health Council. He was a Trustee of the Polytechnic Institute and of the Packer Collegiate Institute. He was a Fellow of the New York Academy of Medicine, and a member of the American Medical Association, the American Heart Association, the National Tuberculosis Association, the Association for the Study of Internal Secretions, the American Society of Tropical Medicine and the American Society for the Advancement of Science.

"Dr. Warren was a Fellow of the American College of Physicians since June 19, 1919, he served as Governor for Eastern New York from 1931 to 1933 and as a Regent from 1933 to the date of his death. His counsel and advice have been of the greatest value to the Board of Regents in shaping the policies of the College. The Board of Regents very deeply mourn his loss and his absence from the Council Table will be very keenly felt, consequently, it is

"RESOLVED, that this Minute in the memory of Dr. Luther Fiske Warren be recorded in the records of the American College of Physicians in appreciation of his services to the College and to the medical profession and that a copy of this Minute be sent to members of his family

—JAMES ALEX. MILLER, M.D., F.A.C.P."

On motion seconded and regularly adopted, it was

RESOLVED, that the above resolutions be adopted and spread upon the Minutes of this meeting

Dr. William Gerry Morgan, as Secretary-General, then presented the following four resolutions on the late Dr. Harlow Brooks, Dr. Ernest E. Laubaugh, Dr. Frank Smithies and Dr. William Alanson White, which, by resolution unanimously adopted, were spread upon the Minutes of this meeting

HARLOW BROOKS

"Whereas, it was the rare good fortune of the American College of Physicians to have had Doctor Harlow Brooks associated with it in membership throughout a period of twenty-three years, and to have enjoyed and profited by his active personal participation and interest in its scientific and other activities

"His broad viewpoint and comprehension of medical problems, and the literary charm and forcefulness of his addresses and papers made his frequent and willing contributions to its programs of unexcelled value to the College. This value was greatly enhanced and enriched by the background of his personality in their presentation and his associations with its membership. Doctor Brooks was a man of great personal charm and friendliness, affable and lovable, a joy and an inspiration, and universally admired, esteemed, and beloved by his associates. The College not only shares in the loss to science and to humanity of this great and good man, but also suffers personal bereavement in the passing of a worthy and beloved personal friend

"And whereas, it is fitting that the College record a testimonial of its appreciation of the life work and character of Doctor Brooks, of its happy personal relations with him over many years, and of its sorrow over his passing, together with an expression of its sympathy with the bereaved family

"BE IT RESOLVED, that we express our deep sorrow for the loss of this true physician and wise counselor

—WILLIAM GERRY MORGAN, M.D., F.A.C.P."

ERNEST E. LAUBAUGH

"Whereas, the American College of Physicians has lost, in the death of Dr. Laubaugh, one of its most devoted Fellows

"Dr Laubaugh died at Boise, Idaho, on December 13, 1936. He was born in Pennsylvania in 1887, and was graduated in medicine from the Medico-Chirurgical College in 1909. After interning at Mercy Hospital in Pittsburgh and later in the Philadelphia General Hospital, he became a member of the Faculty of his Alma Mater. In 1913 he resigned to accept the post of Bacteriologist with the Idaho State Board of Health, a position he held until 1917. At the time of his death, Dr Laubaugh was a member of the Staff of St Alphonsus and St Luke's Hospitals in Boise.

"Dr Laubaugh retired from the World War as Captain in the Army. He was a member of a good many medical and scientific societies and had made notable contributions to medical literature.

"And Whereas, Dr Laubaugh was a former Governor of the College for the State of Idaho and took a keen interest in its welfare and upbuilding.

"BE IT RESOLVED, that the Regents express profound regret for the loss the College has sustained through the death of Dr Laubaugh, and the sympathy which is felt for the bereaved family of the deceased.

—WILLIAM GERRY MORGAN, M D, F A C P"

FRANK SMITHIES

"Whereas, Doctor Frank Smithies passed to his Eternal Home on February 9, 1937, at the age of 56 years. He was born in Elland, England, coming to the United States at the age of 5 years.

"Doctor Smithies was elected to Fellowship in the College in 1917, and throughout the subsequent years he was very active in the participation of its growth and development.

"Doctor Smithies gave unspiringly of his time and energies to the work of the College. To his foresight and directing influence does the College owe not merely its very existence, but the sane lines of its progress.

"Therefore BE IT RESOLVED, that the American College of Physicians through its Board of Regents express the profound regrets and deep sorrow for the loss of this highly valuable and interested Master, who had served as Regent, Secretary-General and President.

—WILLIAM GERRY MORGAN, M D, F A C P"

WILLIAM ALANSON WHITE

"Whereas, Dr William Alanson White died on March 7, 1937, in Washington, D C, in his 67th year.

"Dr White was elected to Fellowship in 1923, and was keenly interested in the progress and welfare of the College. As Superintendent of St Elizabeths Hospital at Washington, he had under his supervision more than six thousand insane patients and over one thousand employees, as well as a large staff of expert physicians. The responsibilities incident to directing such a large and complex institution rendered it impossible for him to attend all of the Annual Meetings of the College, which was a source of profound regret to him.

"Dr White was a man of innate kindness, always ready to extend a helping hand to all who sought his aid. He was universally admired and beloved by his immediate associates, the profession at large and by many in all walks of life.

"And Whereas, it is fitting that the College express its appreciation of the life work and character of Dr White, of his influence for the betterment of his fellowmen, and of its sorrow at his death, together with an expression of its sympathy with the bereaved family.

"Therefore BE IT RESOLVED, that we express our profound sorrow for the loss of this distinguished physician from our membership.

—WILLIAM GERRY MORGAN, M D, F A C P"

Dr George Morris Piersol presented the following resolution on the late Dr James M Anders, which, upon motion unanimously adopted, was spread upon the Minutes of the meeting.

JAMES M. ANDERS

"It is with deep sorrow and regret that we record the death of our distinguished past-president (1922), Dr James M. Anders, of bronchiopneumonia on August 29, 1936

"Dr Anders was a native of Pennsylvania, born on July 22, 1854. After a careful preliminary education he was graduated from the Medical School of the University of Pennsylvania in 1877. His subsequent career proved him to be a worthy son of that celebrated Class which furnished so many outstanding men to the medical profession of this country. The year he graduated in medicine, Dr Anders also received his Ph.D. His early interests centered about the biological and medical sciences. The original investigations which he conducted into certain plant functions earned for him recognition by the French Government, which made him an Officier de l'Instruction Publique et des Beaux Arts.

"Dr Anders attained his greatest distinction, however, in his chosen field of Internal Medicine and Public Health, for which he prepared himself thoroughly by many years of active affiliation with a number of Philadelphia's leading hospitals.

"As a teacher Dr Anders exhibited exceptional ability. In 1889 he became associated with the Medico-Chirurgical College of Philadelphia. By 1893 he had been made Professor of the Theory and Practice of Medicine and Clinical Medicine in that institution—a position which he graced with distinction for twenty-five years.

"Dr Anders' interest in public health and tuberculosis prevention led him to take an active part in civic affairs. From 1914 on he served as a member of the Board of Health of Philadelphia. He became a leading figure in many local, state and national health movements.

"One of Dr Anders' outstanding achievements in medical education was the role he played in bringing about the merge of the Medico-Chirurgical School with the University of Pennsylvania, which resulted in the present Graduate School of Medicine at Pennsylvania. He took an active part in the development and direction of this institution, serving until his death as one of its managers and, through his broad vision and enthusiasm, contributing in no small measure to its growth and success.

"Dr Anders was a prolific scholarly and popular author. In addition to innumerable original articles, he contributed to medical literature his large work on the "Theory and Practice of Medicine," which went through fourteen editions and later a text-book on "Medical Diagnosis." Not content with medical writings, Dr Anders wooed the Muse of poetry, publishing in 1934 a delightful volume, entitled "Meditations in Verse."

"As a reward for his accomplishments in medicine, public health and education, Dr Anders received numerous honorary degrees, was made a Chevalier of the Legion of Honor of France in 1923, and the same year had the distinction of being the first Fellow of this College to be made a Master.

"The crowded, varied, but fruitful career of Dr Anders was marked by signal successes. As a doctor, teacher, author, educator and public spirited citizen, he has earned the gratitude of his chosen City of Philadelphia and left an indelible imprint upon the progress of American Medicine.

—GEORGE MORRIS PIERSON, M.D., F.A.C.P."

Dr Svdnev R. Miller, Chairman of the Committee on Credentials, reported that his Committee had held two meetings—one on March 14, 1937, and one on April 18, 1937. At the meeting on March 14, the credentials of sixty-two candidates for Fellowship were examined. Of this number the Committee recommended the rejection of four, deferment of thirteen for further material time or investigation, and the election of forty-five. Of those recommended for election, thirty-nine were for advancement from Associateship and six for direct election. In one case, a candidate had served a five-year Associate term from 1931 to 1936, but because of critical illness was unable to qualify in the five-year period, and had been dropped. The Committee, however, credited his five-year Associate term and included his name among those for advancement now.

At the meeting of March 14, the Committee examined the credentials of eighty-seven candidates for Associateship, of which they recommended the rejection of ten, the deferment of six and the election of seventy-one.

At the meeting of the Committee on April 18, they considered the credentials of fifty-two candidates for Fellowship, of which they recommended forty-seven for election, one for election to Associateship, and four for deferment for further credentials.

At the meeting on April 18, they also considered fifty-seven candidates for Associateship, of which they recommended forty-seven for election, six for rejection and four for deferment.

The combined recommendations for election of the Committee on Credentials, as included in lists of names passed around for inspection by the Board of Regents, included ninety-two Fellows and one hundred and nineteen Associates.

Upon motion by Dr. Robert A. Cooke, seconded by Dr. Maurice C. Pineoffs, and regularly carried, it was

RESOLVED, that the following candidates shall be and are herewith elected to the respective class of Fellowship or Associateship as recommended:

Elected to Fellowship

Name	City and State
1 Archamberault, Charles Pahl	M C, U S Navy
2 Arkin, Aaron	Chicago, Ill
3 Baehr, George	New York, N Y
4 Baer, Ridgely Waters	Frederie, Md
5 Barry, Michael William	Omaha, Nebr
6 Bergstrom, Victor William	Binghamton, N Y
7 Bernton, Harry Saul	Washington, D C
8 Bishop, F Warner	New York, N Y
9 Boots, Ralph Henderson	New York, N Y
10 Brand, Alonzo Frederick	Fayetteville, N Y
11 Chapman, Edward Northrop	Colorado Springs, Colo
12 Clark, Cyrus J	Indianapolis, Ind
13 Cole, Rufus	New York, N Y
14 Collins, Russell Johnson	East St John, N B, Can
15 Cooke, William Clifford	San Diego, Calif
16 Cooksey, Warren B	Detroit, Mich
17 Curran, Jean A	Brooklyn, N Y
18 Dale, Grover Cleveland	Goldsboro, N C
19 Davies, Willard John	Rockville Centre, N Y
20 DeGraff, Arthur Christian	New York, N Y
21 de la Chapelle, Clarence E	New York, N Y
22 Denny, Earl Rankin	Tulsa, Okla
23 Du Bois, Eugene Floyd	New York, N Y
24 Duggan, LeRoy Bates	Houston, Tex
25 Ecker, Lewis Charles	Washington, D C
26 Ensign, Dwight Chester	Detroit, Mich
27 Fearon, Henry Dana	Brooklyn, N Y
28 Fischer, Carl Castle	Philadelphia, Pa
29 Frissell, Lewis Fox	New York, N Y
30 Geyelin, H Rawle	New York, N Y
31 Goldring, William	New York, N Y
32 Goodwin, George Munro	New York, N Y
33 Gray, George Albert	Sweetwater, Tex
34 Haden, Russell Landram	Cleveland, Ohio

35	Hurmeier, John Watson	Pittsburgh, Pa
36	Henrichsen, Karl Johan	Chicago, Ill
37	Hines, Edgar Alphonso, Jr	Rochester, Minn
38	Hofrichter, Cassius Howard	Seattle, Wash
39	Hookey, John Arlington, Sr	Detroit, Mich
40	Huntington, Herbert Arthur	Los Angeles, Calif
41	Hutton, Robert LeRoy	New York, N Y
42	James, Henry	New York, N Y
43	Jolliffe, Norman	New York, N Y
44	Kitzmiller, Karl Vivian	Cincinnati, Ohio
45	Knowles, George Milton	Hackensack, N J
46	Konrat, Maurice	Staten Island, N Y
47	Krombem, Walter H	Buffalo, N Y
48	Lamb, Albert Richard	New York, N Y
49	Lande, Herman	New York, N Y
50	Larimer, Robert Newell	Sioux City, Iowa
51	Levy, Frank Edward	Philadelphia, Pa
52	Leslie, George L	Howell, Mich
53	Lichty, John Max	Pittsburgh, Pa
54	Lincoln, Asa Liggett	New York, N Y
55	Loeb, Robert Frederick	New York, N Y
56	Marvin, Horace Page	M C, U S Army
57	McAlpin, Kenneth Rose	New York, N Y
58	McEwen, Currier	New York, N Y
59	Mendelson, Joseph A	Tientsin, China
60	Miller, Aura James	Louisville, Ky
61	Moon, Arthur Ernest	Temple, Tex
62	Morgan, Philip Wilhelm	Emporia, Kan
63	Muhl, Anita M	San Diego, Calif
64	Oppenheimer, Bernard Sutro	New York, N Y
65	Patterson, Henry Stuart	New York, N Y
66	Piness, George	Los Angeles, Calif
67	Powell, Vernon Edwin	Atlanta, Ga
68	Railh, Elaine Pandia	New York, N Y
69	Reed, E Burkett	Lincoln, Nebr
70	Remhard, Otto A G	Lincoln, Nebr
71	Rousseau, James Parks	Winston-Salem, N C
72	Russell, Richard Olnev	Birmingham, Ala
73	Ryan, William Joseph	Pomona, N Y
74	Shearer, Leander H	New York, N Y
75	Simons, Samuel Shirk	Lancaster, Pa
76	Smith, Dudley Crofford	University, Va
77	Speed, Henry Kirven	Sayre, Okla
78	Stillman, Edgar	New York, N Y
79	Strong, George Frederic	Vancouver, B C, Can
80	Stygall, James Henry	Indianapolis, Ind
81	Taylor, Kenneth	New York, N Y
82	Tidmarsh Clarence Johnson	Montreal, Que, Can
83	Trump, Frank	Ottawa, Kan
84	Unger, Leon	Chicago, Ill
85	Vogel, Karl	New York, N Y
86	Walker, Hastings Howland	Honolulu, T H
87	Weirauk, Herbert Vanece	Columbus, Ohio
88	Wellman, Harvey Elijah	Providence, R I

89 West, Randolph	New York, N Y
90 Westcott, Franklin Howard	New York, N Y
91 White, Thomas Joseph	Jersey City, N J
92 Woodruff, Isaac Ogden	New York, N Y

Elected to Associateship

Name	City and State
1 Adams, Walter Paul	Norfolk, Va
2 Alexander, Harry Allison	Boulder, Colo
3 Ashley, Claude Wilber	Bloomsburg, Pa
4 Atkinson, Harold Cook	Macon, Ga
5 Badger, Theodore Learned	Boston, Mass
6 Byley, Robert Hebard	New Orleans, La
7 Bell, Joseph Clark	Louisville, Ky
8 Blitch, Clifford Gordon	M C, U S Army
9 Block, Morris	New York, N Y
10 Bohner, Caryle Bernard	Indianapolis, Ind
11 Brown, Marshall Stewart, Jr	New York, N Y
12 Burger, Aaron L	Brooklyn, N Y
13 Cadden, Anthony Vandril	Hopemont, W Va
14 Cannady, Edward Watt	East St Louis, Ill
15 Ceder, Elmer Theodore	U S Public Health Service
16 Chamberlain, Charles Thomson	Fort Smith, Ark
17 Chilko, Alexander J	New Rochelle, N Y
18 Cooper, Henry Lewis	Denver, Colo
19 Culp, John Ewart	Ithaca, N Y
20 Dixon, Ira Milburn	Stockbridge, Mass
21 Dozzi, Daniel Louis	Philadelphia, Pa
22 Driscoll, Charles Dennis	Haddon Heights, N J
23 Dyrenforth Lucien Young	Jacksonville, Fla
24 Falisi, James Vincent	M C, U S Army
25 Farrar, George Elbert Jr	Philadelphia, Pa
26 Fatherree Thomas Jefferson, Jr	Rochester, Minn
27 Findley Thomas Palmer, Jr	St Louis Mo
28 Fink, Harold	Brooklyn, N Y
29 Finnigan, Francis Roman	St Louis, Mo
30 Foley, Maurice P	Rochester, Minn
31 Foster, Frank Pray	Rochester Minn
32 Fuendeling, Mervyn Julius	Twin Falls, Idaho
33 Gandara, Jose Nicolas	Ponce, P R
34 Glenn, Elmer Edward	Springfield, Mo
35 Gosline, Harold Inman	Ossining, N Y
36 Goodrich, Murray Eugene	Toledo, Ohio
37 Greenhouse, Barnett	New Haven, Conn
38 Gutman Alexander B	New York, N Y
39 Hall, Byron Ellsworth	Rochester Minn
40 Hammonds, Everett England	Birmingham, Mich
41 Harris, Robert Miller	Miami, Fla
42 Hart Andrew DeJarnette, Jr	Charlottesville, Va
43 Hausheer, Walter C	Staten Island N Y
44 Hedley, Oswald F	U S Public Health Service
45 Hemingway, Max William	Bend, Ore
46 Hershenson, Morris A	Pittsburgh, Pa
47 Houch, George Hamilton	Los Angeles, Calif

48 Hutton, John Evans	New York, N Y
49 Jacobs, Minnie F	Oklahoma City, Okla
50 Johnson, Alf Cornelius	Great Falls, Mont
51 Jukes, R Franklin	Akron, Ohio
52 Kandel, Harry Milton	Savannah, Ga
53 Katzman, Maurice	Denver, Colo
54 Kendall, Charles Benjamin	M C, U S Army
55 Kinney, James P	Buffalo, N Y
56 Kneeland, Yale, Jr	New York, N Y
57 Koons, Ruth Alice	Columbus, Ohio
58 Lake, Michael	New York, N Y
59 Langdon, Roy Luther	Philadelphia, Pa
60 Lansbury, John	Philadelphia, Pa
61 Ledbetter, Abbe Alzu	Houston, Tex
62 Leser, Ralph Ulrich	Bloomington, Ind
63 Lewis, William Hall, Jr	New York, N Y
64 Lieberman, John F	M C, U S Army
65 Logie, Arthur J	Jacksonville, Fla
66 Madden, Lucius Emmett	Columbia, S C
67 Mahon, Hugh William	M C, U S Army
68 Margulis, Aaron E	Mount Morris, N Y
69 Martin, George Graddon	Buffalo, N Y
70 McCall, Marsh	New York, N Y
71 McGrath, Robert	New York, N Y
72 Monroe, Robert Thornhill	Brookline, Mass
73 Morales, Luis M	Santurce, P R
74 Morlock, Carl Grismore	Rochester, Minn
75 Murphy, Robert Gordon	Providence, R I
76 Nichol, Arthur Dale	Cleveland, Ohio
77 Nicklas, John M	Valhalla, N Y
78 Nickum, John Stanley	Bridgeport, Conn
79 Noyes, Edward Allen	M C, U S Army
80 Olson, Andrew Allen	Wichita, Kan
81 Ormond, Alexander Pierce	Akron, Ohio
82 Paley, Samuel S	New York, N Y
83 Parker, Robert Lawrence	Rochester, Minn
84 Perakos, George	Philadelphia, Pa
85 Persons, Elbert Lapsley	Durham, N C
86 Peters, John	Maywood, Ill
87 Poole, Wallace L	Johnson City, Tenn
88 Prince, Homer Edward	Houston, Tex
89 Redelings, Leslie Hall	San Diego, Calif
90 Richards, Calvus Elton	Gallipolis, Ohio
91 Robb, George Porter	New York, N Y
92 Rudesill, Cecil Logan	Indianapolis, Ind
93 Russman, Charles	Middletown, Conn
94 Salkin, David	Hopemont, W Va
95 Sander, Oscar A	Milwaukee, Wis
96 Schwartz, Jacob	Brooklyn, N Y
97 Scovel, Frederick Gilman	New York, N Y
98 Sharkey, Thomas Palmer	Davton, Ohio
99 Sharp, Ezra Abraham	Providence, R I
100 Solomon, Charles	Brooklyn, N Y
101 Solomon, Reuben A	Indianapolis, Ind

102 Sours, James W	Peoria, Ill
103 Sparks, Munroe Irving	Cleveland, Ohio
104 Steinberg, Israel	New York, N Y
105 Strickler, Cyrus Warren, Jr	Atlanta, Ga
106 Sugarman, Harold	Saskatoon, Sask, Can
107 Torbett, John Walter, Jr	Marlin, Tex
108 Townsend, James Harvey	Boston, Mass
109 Tripp, Carl Edward	Boston, Mass
110 Ulmar, David	New York, N Y
111 Van Buren, Ebert	Atlanta, Ga
112 Walker, George Leonard	Griffin, Ga
113 Wallace, Robert Pulley	New York, N Y
114 Walsh, Edmund Michael	Omaha, Nebr
115 Ward, Albert Gayden	Jackson, Miss
116 Weinstein, Albert	Nashville, Tenn
117 Weinstein, Joseph	Brooklyn, N Y
118 Wilder, Gordon Botkin	Anderson, Ind
119 Woldman, Edward Elbert	Cleveland, Ohio

Dr Sydney R Miller, as Chairman of the Committee on Credentials, further reported that they recommend to the Board of Regents that the name of Dr Fernando Ocaranza, of Mexico, D F, be dropped from the Roster of Fellows, because he had failed to take up his election to Fellowship by the payment of the prescribed fees and dues in accordance with the By-Laws

On motion by Dr Sydney R Miller, seconded by Dr James E Paullin, and regularly carried, it was

RESOLVED, that the name of Dr Fernando Ocaranza, Mexico, D F, be dropped from the Roster of Fellows because of failure to take up his election in accordance with the Constitution and By-Laws

Dr Sydney R Miller, as Chairman of the Credentials Committee, presented the following resolution which had been unanimously adopted by his Committee at their meeting in Philadelphia on March 14

RESOLVED, that reconsideration of the proposed amendments to the Constitution and By-Laws be gone into by the Board of Regents before being proposed at the Annual Session

President Bradley explained that the members of the Credentials Committee have a very deep interest in the question of changes in the standards of admission anticipated by amendments proposed at the December, 1936, meeting of the Board, and felt particularly that the provision that certification should be a prerequisite for Associateship should be reconsidered, also the matter of "affiliated specialties"

On motion by Dr Bierring, seconded by Dr Means, and regularly carried, the resolution presented by the Committee on Credentials was adopted

There followed open discussion concerning the amendments proposed to the Constitution and By-Laws at the Regents' meeting during December, 1936

Dr James Alex Miller expressed regret that Dr Jonathan C Meakins, a member of the Committee on Constitution and By-Laws, was not present to join in the discussion. Dr Miller said that he thought it premature to put the proposed amendments into effect, for the reason that the question of certification of internists has not yet been established on a firm footing. If the Credentials Committee continues as it has in the past to closely scrutinize the credentials of every candidate, and even to more carefully investigate their credentials, the College may proceed on its present basis, giving the American Board of Internal Medicine more time to get established. The College should at least preserve its independence of action, and in his opinion the Board might do well to withdraw both the proposed amendments until some later time.

Dr Walter L Bierring, Chairman of the American Board of Internal Medicine, dis-

cussed the proposed amendments adopted during December, 1936, and suggested that certification might more properly be made a prerequisite for Fellowship, rather than for Associateship. He reported that to that date eighty-six applicants had applied for the examinations of the Board, and prophesied that in three or four years the Board may be called upon to examine about two hundred candidates a year, which is about the same as the number of elections to Fellowship in the College.

In part, Dr. Biering said "The type of Fellows of the College would be such as had been certified as internists under the proposed newer regulations. It is difficult to formulate any kind of a plan that would include distinguished men who would not come under the head of certified internists, whom we would feel honored to have made Fellows of this College, whether they were in an allied field or not, and it seems to me they should be in, if they can qualify. But, the American College of Physicians is an association of internists, as we understand it, and we feel that we might approximate somewhat to the standards and ideals of the Royal College of England and Scotland, if an examination is one of the qualifications for election. It is true that these Colleges also elect to Fellowship obstetricians, pediatricians, neurologists and other allied branches of Internal Medicine, not surgical."

Chairman Bradley pointed out that at the present time the American College of Physicians is not for internists only, but for those engaged in internal medicine and allied specialties.

At this point, Dr. Alfred Stengel, Acting Chairman of the Committee on Constitution and By-Laws, was called upon to make a report.

After discussing various considerations that had been presented to the Committee, Dr. Stengel summed up his remarks by saying that "it was the recommendation that the Board of Regents withdraw from the proposed amendments altogether at this time, because they feel the action is premature."

Dr. Stengel pointed out that another proposal had been received by the Committee, namely, to make provision for the legalization of alternates for the members of the Board of Governors who may be unable to attend the Annual Meetings. The following amendment had been formulated by Dr. Jonathan C. Merkins, the Chairman of the Committee:

"Any member of the Board of Governors unable to attend the Annual Session shall appoint as his alternate, with all the privileges of a Governor, a Master or Fellow of his district who will be in attendance at that Session. Upon presentation to the Chairman of the Board of Governors of a certificate of appointment, the alternate shall be recognized and act in the full capacity of Governor for the Session to which he has been appointed. The same alternate shall not be appointed for more than two consecutive years."

This amendment had not previously been presented to the Board of Regents for approval.

Dr. Stengel recommended that if the other recommendations for alterations in the Constitution and By-Laws are to be laid on the table for the present, it might be well to defer action also on the above proposal until another year.

On motion by Dr. Walter L. Biering, seconded by Dr. Sydney R. Miller, it was

RESOLVED, that the Board of Regents, after thoroughly studying the situation, withdraw the proposed amendments to the Constitution and By-Laws as considered at the December, 1936, meeting of the Board and subsequently published in the "Annals of Internal Medicine", and, further, any other amendments for action at the Annual Business Meeting during the current year.

In the discussion of the resolution, Dr. Maurice C. Pincoffs said in part, "These amendments have been read by all the members. That need not influence the Board in any way, but I think the motion before the house is something I favor, but I would like to present one point about it before we act, namely, there are a number of other solutions to these problems. We can make the certification a necessity or prerequisite for election for Fellowship

for men who are practicing Internal Medicine, and put up some other qualifications for those who are practicing affiliated specialties. Many of these affiliated specialties have Boards of their own, and we could equally well make it necessary for candidates from those specialties to present certification by their Boards before being elected by the College, so that we do not implicate or do not necessarily commit the College not to admit men in these other specialties, when we demand that those who are internists be certified. I feel certain that if we do not require our Fellows at least to be certified, before any great lapse of time, we would be withdrawing support from the American Board of Internal Medicine, an organization that we have sponsored."

Dr O H Perry Pepper recommended that there should be published in the "Annals of Internal Medicine" some explanatory statement concerning the action taken by the Board of Regents.

There followed discussion among the Regents generally concerning an official statement to the members at the Annual Business Meeting.

The following resolution was also regularly adopted:

RESOLVED, that a Committee of three, consisting of the President, Dr Walter L Biering, Chairman of the American Board of Internal Medicine, and Dr Maurice C Pincoffs, Editor of the ANNALS, shall be empowered to draw up an explanatory statement of the action of the Board of Regents for presentation to the members at the Annual Business Meeting.

Dr O H Perry Pepper, Chairman of the House Committee of the College, reported verbally that minor alterations and final furnishing had been completed since the last meeting of the Board of Regents, and that the balance from the appropriation made at the December meeting amounted to \$617. He said the Committee felt that the building is completed, that it is completely furnished, and that the Committee might well be discharged, the continued care of the building being left in the hands of the Treasurer and the Executive Secretary.

The Executive Secretary, Mr Loveland, said that he felt the Committee might very well be continued, for it would be helpful to have an official Committee with whom to consult.

On motion, seconded and regularly carried, it was:

RESOLVED, that the House Committee be tendered the thanks of the Board of Regents for their work, and that the Committee be continued.

President Bradley then asked Dr Stengel if there were any additional reports to be presented by the Committee on Constitution and By-Laws.

Dr Stengel stated that the only matter not officially acted upon was the proposed amendment providing for alternate Governors.

After general discussion, the following resolution was moved, seconded and regularly carried:

RESOLVED, that the following paragraph be added at the end of Article IV, Section 1, of the By-Laws, and that notice of the proposed addition to the By-Laws be published in the ANNALS OF INTERNAL MEDICINE at least one month in advance of the next Annual Business Meeting in 1938:

"Any member of the Board of Governors unable to attend the Annual Session shall appoint as his alternate, with all the privileges of a Governor, a Master or Fellow of his district who will be in attendance at that Session. Upon presentation to the Chairman of the Board of Governors of a certificate of appointment, the alternate shall be recognized and act in the full capacity of Governor for the Session to which he has been appointed. The same alternate shall not be appointed for more than two consecutive years."

President Bradley stated that a number of members had suggested the propriety of having a history of the College written to date, while there are still members thoroughly conversant with all the past details since organization. Dr Bradley thereupon appointed Dr William Gerry Morgan to write such a history at his leisure.

On motion by Dr James Alex Miller, seconded by Dr Pepper, and regularly carried, it was

RESOLVED, that the Committee on Nominations take under consideration the nomination of a Governor for the State of South Dakota, since that State now qualifies to have its own Governor

Dr Walter L Bierring, Chairman of the American Board of Internal Medicine, reminded the Board of Regents that each one is an Adviser to his Board. He reported that the Board had in its files 1,030 applications for certification without examination. They had been arranged by states and cities, and the Board desires as much advice from the Regents as possible in the valuation and determination of the eligibility of these applicants. Dr Bierring also referred to refunding to the American College of Physicians, in partial payments in annual allotments, the loan that had been made to the American Board of Internal Medicine.

Dr Pepper suggested no action be taken until the American Board of Internal Medicine had further opportunity of reviewing their finances and determining upon a definite refunding plan.

On motion by Dr Pepper, seconded and regularly carried, it was

RESOLVED, that the sum of \$100.00 be appropriated for the uses of the College Historian, should he find need of extra clerical assistance, or in any other matters connected with preparing the history of the College.

Adjournment

Attest E R LOVELAND,
Secretary

MINUTES OF THE BOARD OF REGENTS

St Louis, Mo

April 20, 1937

The second meeting of the Board of Regents, during the Twenty-first Annual Session, was held at the Jefferson Hotel, St Louis, April 20, 1937, with President Ernest B Bradley presiding and the Executive Secretary acting as secretary of the meeting. On the calling of the roll, the following were recorded as present:

Ernest B Bradley, *President*,
James H Means, *President-Elect*,
O H Perry Pepper, *First Vice-President*,
Walter L Bierring, *Third Vice-President*,
William Gerry Morgan, *Secretary-General*,
William D Stroud, *Treasurer*,
William J Kerr,
Roger I Lee,
Sydney R Miller,
George Morris Piersol,
G Gill Richards,
Robert A Cooke,
James B Herriek,
Hugh J Morgan,
James E Paullin,
Egerton L Crispin,
James Alex Miller,
Francis M Pottenger,
Charles H Coeke,
Maurice C Pineoffs

Upon motion, seconded and regularly carried, the reading of the Minutes of the previous meeting was dispensed with

Chairman Bradley called for the presentation of additional resolutions

Dr William Gerry Morgan, as Secretary-General, presented the following resolution on the death of Dr Henry F Stoll, as prepared by Dr George Blumer, Governor for Connecticut

HENRY FARNUM STOLL

"Whereas The Almighty, in his inscrutable wisdom, has seen fit to remove from our midst our friend and colleague, Henry Farnum Stoll, and

"Whereas In his unstinted devotion to duty, his lively appreciation of the importance of the public as well as the private aspects of medical practice, his constant efforts to extend the limits of knowledge in his field, and his vital interest in the welfare of his patients he exemplified the best traditions of the medical profession, therefore,

"BE IT RESOLVED, that we place upon our Minutes a record of our sorrow at his passing and our appreciation of his many admirable qualities, and that we extend to his family our heartfelt sympathy

—GEORGE BLUMER, M D, F A C P "

On motion, seconded and regularly carried, the above resolution was adopted

Dr Morgan then presented the following resolution, prepared by Dr David P Barr, on the death of Dr W McKim Marriott

WILLIAM MCKIM MARRIOTT

"William McKim Marriott, Fellow and former Regent of the American College of Physicians, died on November 11, 1936 He was Professor of Pediatrics and for thirteen years was Dean of the School of Medicine at Washington University As teacher and investigator, he achieved an international reputation As a medical administrator, he saw with clarity the great problems of medical education in a rapidly changing practice Although possessed of a fine critical faculty, he was generous and tolerant of the weaknesses and faults of others To a remarkable degree, he was able to see the point of view of his colleagues, to reconcile conflicting opinions, to clarify issues and to accomplish joint action Above all, he was imbued with a spirit of optimism which enabled him to ride over difficulties, to proceed after defeat and to pursue under most adverse circumstances the ideals to which he was devoted

"Dr Marriott's training had not been that of an administrator He had prepared himself as a chemist, a pediatrician and a teacher It was in these directions that he had progressed during his youth With his numerous executive duties, with the never-ending exactions of the Dean's Office, he was able to continue the work for which he was especially qualified It was during the period of his Deanship that his semi-annual course in pediatrics became one of the most important single factors in the postgraduate training of specialists in diseases of children He served on the editorial board of the American Journal of Diseases of Children He prepared and published lectures on 'Recent Advances in Chemistry in Relation to Medical Practice' He published his classical monograph on 'Infant Nutrition' On the busiest days he was able to make his rounds in the hospital, to supervise the innumerable activities of one of the most productive departments of pediatrics in the world At one time he was an officer in the Southern Medical Association He served effectively on the Council of Pharmacy and Chemistry of the American Medical Association He was active in the formation of the Council on Foods In the midst of all this activity, it was remarkable that he was never too busy to be available to the younger men of his staff, and was never too pre-occupied to offer them inspiration, guidance and help from his great experience From among his pupils, universities have chosen men to fill some of the most important positions in the field of pediatrics

"Dr Marriott possessed one of the great medical minds of our generation In the

breadth of his vision he had few equals. His profundity in diverse fields is attested by his achievements.

"The American College of Physicians was fortunate to have him among those who have made it one of the great medical organizations. It grieves with others in the loss of one of the great leaders in medicine and in the world of science.

—DAVID P. BARR, M.D., F.A.C.P."

On motion, seconded and regularly carried, the above resolution was adopted.

Dr. James E. Paullin, Chairman of the Committee on Public Relations, presented the following report and recommendations:

(1) That the following resignations be accepted:

Dr. Daniel F. Milam (Fellow), Hastings-on-Hudson, N. Y.

Dr. Bernard A. Manace (Associate), Toronto, Ont.

Dr. Vincent D. King (Associate), Memphis, Tenn.

Dr. Edward L. Voke (Associate), Akron, Ohio.

Upon motion by Dr. William Gerry Morgan, duly seconded and carried, it was

RESOLVED, that the resignations of Doctors Milam, Manace, King and Voke be accepted.

(2) The Committee recommended that the resignation of Dr. Frederick H. Lamb (Associate), Davenport, Iowa, be held in abeyance, pending further correspondence with Dr. Walter L. Bierring, in view of the fact that the Governor for Iowa had not furnished sufficient data to enable the Committee to make a recommendation.

Upon motion by Dr. William Gerry Morgan, duly seconded and carried, it was

RESOLVED, that the resignation of Dr. Frederick H. Lamb (Associate), Davenport, Iowa, be held in abeyance, pending further correspondence with Dr. Walter L. Bierring.

(3) The Committee recommended that the dues of Major F. R. Borden (Fellow), M. C., U. S. Army, retired, be remitted because of physical disability.

On motion by Dr. James Alex. Miller, duly seconded and regularly carried, it was

RESOLVED, that the dues of Major F. R. Borden, M. C., U. S. Army, be remitted because of physical disability.

(4) The Committee recommended that the letter of Dr. E. M. Stevenson, of Bloomington, Ill., be returned to the Executive Secretary without comment.

Upon motion, seconded and regularly carried, the entire report of the Committee on Public Relations was adopted.

Dr. James Alex. Miller reported, as Chairman of the Committee on Future Policy for the Development of Internal Medicine, as follows:

"A meeting of the Committee on Future Policy for the Development of Internal Medicine was held on April 19, 1937. There were present Dr. James Alex. Miller, Chairman, Dr. F. M. Pottenger, Dr. Maurice C. Pincoffs, and Dr. Roger I. Lee.

"The various proposals concerning the future policy of the College were considered, and, in general, it was the consensus of opinion that the chief emphasis in future policy should be upon efforts to improve postgraduate education in Internal Medicine in this country, and, particularly, for Fellows and Associates of the College.

"1 The suggestion that the College set up a revolving loan fund to aid candidates for certification by the American Board of Internal Medicine, so that candidates might be enabled to undertake studies which would fit them to meet the requirements of these examinations was recommended as worthy of approval by the Regents if and when the financial resources permit.

"2 The recommendation that the College establish lectureships to be given by outstanding internists, both from foreign countries and the United States, was considered, but the Committee does not deem it wise at the present time at least to recommend this as a policy for the College.

- "3 Dr Herman Mosenthal presented a proposition for the establishment of regular short courses for postgraduate students in Internal Medicine in certain selected medical centers. It was Dr Mosenthal's suggestion that the College consider the appropriation of a sum of money to provide for an executive secretary to organize and administer such courses. This proposition was not approved by the Committee.
- "4 It was brought to the attention of the Committee that a tentative movement is on foot to provide a survey of all postgraduate facilities in the United States and that it had been intimated that funds for conducting such a survey might be available, if the need for it was indicated on the part of representative medical organizations. The Committee voted to recommend to the Regents that they approve a plan for such a national survey of postgraduate facilities as far as it relates to Internal Medicine, provided that the survey was planned and conducted under suitable auspices and provided that as a part of the survey some plan for a continuing organization which would afford opportunities for information and guidance for prospective postgraduate students was proposed.
- "5 The Committee thoroughly discussed the desirability of the College doing something of a specific nature to provide postgraduate courses for its Fellows and Associates. As a result of this discussion, it was specifically recommended that the Board of Regents consider the feasibility of providing special short courses in various branches of Internal Medicine to be held at about the time of each Annual Session. These courses to be organized both in the city where the Session is held and in conveniently located near-by medical centers. It was suggested that such courses might be of two weeks' duration and be conducted either immediately before or immediately after the week of the general Session. It was also recommended that the Regents consider giving some financial assistance to the organization of such courses, so that any fees that were charged could be kept very low. It was specifically suggested that an assistant to Mr Loveland might be provided to take charge of this work.
- "6 The Committee also discussed the policy the College should have in the future toward its commercial exhibits. It is the opinion of the Committee that the character of the commercial exhibits should be kept of a very high order, and that the College should bear in mind that in the future it should not be wholly dependent upon the income from the commercial exhibits so as to in any way influence the character of the exhibits. Toward this end, it was suggested that the Board of Regents might appoint a subcommittee to make a special study of this question.
- "7 The general question of the future policy of the College, as it relates to membership in the various allied specialties and, particularly, as it relates to the policy of the College toward the American Board of Internal Medicine was discussed. It was the sense of the Committee that the action in delaying the proposed changes in the Constitution and By-Laws concerning these questions is wise but the Committee wishes to emphasize to the Board of Regents its strong feeling that the policy of the College should gradually extend toward a raising of standards which eventually might reach the standards set in the proposed amendments, to the end that the standards of practice in Internal Medicine in general may be raised and that Fellowship in the College may be increasingly considered as an honor.

"In connection with the problem of the allied specialties, it was the feeling of this Committee that the retention of a certain number of Fellows representing these specialties would be desirable, but that in the future any applications for Fellowship in this class should be scrutinized with especial care and should ultimately probably require the certification of each candidate by his own special National Board or, lacking that, its equivalent in professional or scientific achievement."

Discussion of the Report

Item four Dr Miller explained that this proposal is simply a matter as to whether the Board of Regents desires to place on its Minutes the approval of the recommendation of

the Committee that there should be considered, under proper safeguards, a survey of post-graduate facilities in Internal Medicine. Dr. Miller said his Committee was unanimously in favor of it, and offered a resolution that the recommendation be adopted. The motion was seconded by Dr. Kerr.

In the discussion of the motion, it was again pointed out that the recommendation could not be made more specific at the present time, because the plan will come back again when it is consummated, but, in order to get the survey started, a few medical organizations would have to say that they think such a survey, properly conducted, would be desirable.

Chairman Bradley inquired about the source of funds for such a survey. Dr. Miller replied that funds might be provided from two of the large foundations, but these foundations would wish to know first whether the American College of Physicians and the New York Academy of Medicine believe such a survey would be useful and desirable.

Dr. Pincoffs suggested that this motion should be sent to the Council on Education of the American Medical Association, so that the College would be dealing at once with them, and with any one else who might be interested in such a survey, showing that the resolution by the College does not designate any foundation, but merely indicates the desirability of such a survey, under proper auspices.

The motion was then put to vote and regularly carried.

RESOLVED, that the American College of Physicians approve in principle that a survey of all postgraduate facilities of the United States would be desirable, so far as it relates to Internal Medicine, providing that the survey be planned and conducted under suitable auspices, and providing that as a part of the survey, some plan be proposed for a continuing organization, which will afford opportunities for information and guidance for prospective postgraduate students.

Discussing recommendation "five" of the Committee, Dr. Miller said:

"This is a very far reaching suggestion looking toward an effort to do something specifically for our College members, and to do it in a way which they would feel in a large part is a contribution open to them because of their Associateship or Fellowship in the College, and an opportunity to extend the College's postgraduate activities. These courses would be open only to Associates and Fellows of the College. It would be determined in advance what courses are available in the city, or near-by cities, where our courses would be conducted. The members of the College would have to be circularized through the 'Annals,' and in every other way. It might add to the prestige of the College, and we hope it would add to the services extended to our membership. We were hoping that the fee charged might be a nominal one, perhaps \$10.00. The proposal involves a consideration of honoraria to those giving the courses, or, perhaps, from the beginning the plan might be tried on an honoraria basis. The plan might involve the appointment of an assistant to the Executive Secretary who would be competent to do some medical work in the College. The courses would naturally be organized by a local group, but could be organized in any manner desired, with the courses being offered not only by Fellows of the College, but by others who might be selected.

"The recommendation before the Regents, first, requires the approval of the principle, and, secondly, requires consideration of ways and means of carrying it out and expenditures therewith involved. If approved, the proposal probably involves the appointment of a special committee. It seems to me that today we might go so far as to approve the principle of giving such services to our Fellows and Associates, by these short courses at about the time of the Annual Sessions. If this proposal should be undertaken next year, and the Annual Meeting should be held in New York City, courses could readily be organized, using the facilities of New York, of Philadelphia, of Boston, and of New Haven, at least for such clinics. There should be no great difficulty in organizing two-week courses in all the various branches of Internal Medicine. I move the approval of the Board of Regents of the project as a desirable activity of the

College, and the appointment of a special sub-committee to be concerned solely with the project"

The motion was seconded by Dr William Gerry Morgan

In the discussion, Dr Miller pointed out that if expenditures should be involved, the Executive Committee of the Board of Regents has power, in the interim, to act on all necessary expenditures

Dr James E Pullin expressed his hearty approval of the proposal, but asked that the Committee might even broaden its scope. There have been springing up all over the country various postgraduate courses. The College might be able to serve a very useful purpose, and instead of limiting its postgraduate activities to just before the Annual Meeting, it could sponsor, conduct and supervise postgraduate courses in the various districts of the country, bringing the courses near at hand to the members, and not requiring so much of their time for the Annual Meetings, often conducted at a long distance removed from their homes

Dr Miller pointed out that in his opinion, for the first year or two, the College might better confine its activities to one set of courses, perfect its method of organization, get more experience, and then probably expand the principles if it works out successfully. Furthermore, by that time, the survey of postgraduate facilities might be completed, and the Committee probably could report back on further procedure

The motion was then put to a vote, and unanimously carried

RESOLVED, that the Board of Regents approve of the feasibility of providing special postgraduate courses in various branches of Internal Medicine to be held at about the time of each Annual Session, these courses to be organized both in the city where the Session is held and in conveniently located, near-by medical centers, further, that the Board of Regents approve the appointment of a special sub-committee to be concerned solely with this project

In further commenting upon the action taken, Dr Pincoffs suggested that the members of the Board and the committee, when appointed, consider the project carefully, so that they will be ready for definite action at the 1937 autumn meeting of the Board of Regents

Dr James Alex Miller pointed out that the committee should bear in mind that there is a definite implication that the fees charged to our members should be kept as low as possible

Dr Miller further said that the medical assistant might find many avenues of service to the College which might materially strengthen the Organization

In discussing item "six" on the report of the Committee concerned with the matter of commercial exhibits and advertising, Dr Miller emphasized the need for a complete study of both exhibits and advertising, with a view to keeping both on the highest possible plane. In regard to exhibits, the suggestion was made that perhaps they could be somewhat more restricted in their extent, with the elimination of any exhibit that is not specifically relevant to the practice of Internal Medicine, or one of its affiliated specialties

Upon motion by Dr James Alex Miller, seconded by Dr William Gerry Morgan, and regularly carried, it was

RESOLVED, that the Committee on Advertising and Commercial Exhibits, as presently constituted, be terminated, and that a new Committee be appointed by the incoming President, the duties of the Committee to make a survey and to formulate future policies for the acceptance of advertisements in the "Annals of Internal Medicine" and the acceptance of exhibits for our Annual Sessions

No action was required on item "seven" of the Committee's report. However, item "one" on the report not previously discussed, was again reviewed, namely, the setting up of a revolving loan fund to aid candidates seeking certification by the American Board of Internal Medicine enabling them to undertake studies which would fit them to meet the requirements of these examinations

Dr Maurice C Pincoffs, speaking on the matter, said "It occurs to me that the College is playing a considerable part in making it harder for men to enter Internal Medicine, and

that we stand in not a little danger of having our internists selected by their financial capacity, rather than by their character and by their brains. The College might well do something to help some of these younger men who may be crowded out of the career of Internal Medicine, though they are well fitted for it in every other way than finances. There are throughout the country a great number of revolving loan funds in connection with undergraduate and, to some extent, graduate work. There is in New York a foundation which itself operates such a fund, and which has made a study of the broader question of revolving loan funds. While we may not be able to take action today, it seems to me a project well worthy of studying, and a committee might be appointed by the President to obtain the assistance of that foundation, which was offered gratis and very willingly, in working out a definite and specific plan on the basis of its experience with revolving loan funds in general among students and graduates; the committee to submit their findings at the autumn meeting of the Board of Regents, so that the matter may be considered in terms of experience, in dollars and cents, in relation to our finances."

On motion by Dr. Pincoffs, seconded by Dr. Kerr, it was

RESOLVED, that the Board of Regents shall appoint a special committee for the purpose of studying the question of the operation of revolving loan funds for medical graduates preparing for certification.

Speaking to the motion Dr. Kerr said in part: "One of the problems confronting us is that a number of younger men who are encouraged, and, perhaps, expected, to spend a year or more in one of the basic sciences or fundamental branches of medicine, after their medical school years may not be able to do so. It, therefore, seems to me if we could provide the means for this in some measure through a loan fund, we would reap the benefits. I was very much impressed by the recommendations of the Committee on Future Policy for the Development of Internal Medicine in other directions, looking toward postgraduate education. I think they are all in the right direction, and it seems to me that the College is now beginning to have some real objectives, objectives that our Governors and Fellows have been looking for us to establish."

The motion was put to a vote and unanimously adopted.

The appointment of the Committee was left to the incoming President.

On motion by Dr. Paullin, duly seconded and carried, it was

RESOLVED, that the Board of Regents adopt the report, as a whole, of the Committee on Future Policy for the Development of Internal Medicine.

Dr. Pincoffs had no specific report as Editor of the ANNALS OF INTERNAL MEDICINE, saying that his report will be covered by the report of the Committee on the ANNALS, which will be given by the Chairman, Dr. Means.

Dr. James H. Means, Chairman of the Committee on the ANNALS, reported that a meeting had been held with all members of the Committee present, and with the Editor, Dr. Stroud and Dr. Pepper present by invitation. The affairs of the ANNALS had been discussed with the Editor, and no specific recommendations were presented. The chief item of consideration had been that of festschriften, particularly a festschrift for Dr. Joseph H. Pratt, of Boston. The Editor's policy in regard to the handling of festschriften was considered further by the Committee.

At this point, Dr. Pincoffs explained that in selected cases where an anniversary volume is to be published in honor of some outstanding medical authority, certain of the articles might be accepted for publication in the ANNALS OF INTERNAL MEDICINE, so that they may have a permanent place in medical literature, the right to be reserved to publish only such of those articles as the Editor might feel meet the standards of the ANNALS. They will be published with a modest heading, explaining that they are to form a part of an anniversary volume. The College, or the ANNALS, will take no part in organizing or sponsoring a festschrift to any one, merely adopting the policy of publishing in the ANNALS, under proper heading, suitable material from such festschrift. The ANNALS may gain considerable valuable material in this manner. The first articles from the festschrift of Dr. Joseph H. Pratt,

of Boston, marking his sixty-fifth birthday, will appear in the May, 1937, issue of the ANNALS, and continue through December. The committee in charge of the festschrift has made its own arrangements with our publishers, so that the type from these articles in the ANNALS can later be used in publishing its volume, to which will probably be added such other festschrift articles as have not been accepted for the ANNALS. Dr. Pineoffs said that it is his belief that this is the first time any medical journal has undertaken this matter, and expressed the hope that it is going to have some merit in adding to the value of festschrifts in the future. So often they are a total loss to medical literature.

Dr. Walter L. Bierring reported that the American Board of Internal Medicine had discussed the method of refunding its financial obligation to the College, and that it had taken action authorizing the refunding to the College at this time \$5,000.00 of its loan and a check for said amount was delivered to the College.

Dr. William D. Stroud, Treasurer, presented the following report:

"To the Board of Regents

"As of March 31, 1937, the College has invested securities of a book value amounting to \$101,857.00, of this amount, \$58,853.00 is in the Endowment Fund and \$43,004.00 is in the General Fund, \$82,250.00, or 80.75% of the above amount is invested in bonds, \$4,741.00, or 4.65% is invested in preferred stocks, and \$14,866.00, or 14.60% is invested in common stocks. In addition, the college has in bank balances \$47,470.00, making a total of \$149,328.00 as compared with a total of \$157,329.00 approximately one year ago at the time of the last yearly meeting.

Respectfully submitted,

(Signed) WILLIAM D. STROUD, *Treasurer*"

He pointed out that in spite of having purchased the new College Headquarters and having paid for the improvements and furnishings, the invested capital of the College was only \$8,000.00 less than a year previous.

Upon motion by Dr. James Alex. Miller, seconded by Dr. William Gerry Morgan, it was RESOLVED, that the report of the Treasurer be accepted and placed on file.

Dr. James Alex. Miller, as Chairman of the Committee on Finance, presented the following report:

"A meeting of the Finance Committee was held on April 19, 1937. There were present Dr. James Alex. Miller in the Chair, Dr. Roger I. Lee and Dr. William D. Stroud.

"The financial statements were submitted by the Treasurer and by the Executive Secretary, and also an analysis of the present investment list by the Investment Counsel. Upon recommendation of the Treasurer and of the Executive Secretary, it was decided that \$15,000.00 might be safely withdrawn from the available cash funds in the General Fund for investment. It was voted to approve the investment of this amount for the General Fund account in securities later to be approved upon the recommendation of the Investment Counsel. Upon recommendation of the Investment Counsel, the sale of \$5,000.00 of Chesapeake and Ohio, 3½s, due 5-1-96 was authorized. This is for the Endowment Fund account. Also, upon the recommendation of the Investment Counsel, it was authorized to sell the following:

50 Shares General Motors Corporation, common
45 Shares Mid-Continent Petroleum Corporation
70 Shares National Breweries, Ltd., common

These three transactions are for the General Fund account.

"Also, it was voted to authorize to buy for the Endowment Fund account \$5,000.00 of Northern States Power Company, First Refunding 3½s, due 2-1-67. It was also voted to buy for the General Fund account, 50 Shares of Chase National Bank of New

York, common stock, and 30 Shares of Pacific Gas and Electric Corporation, 6%, cumulative preferred

"The recommendation of the Investment Counsel to invest the remaining \$3,300.00 realized from the above sales for the General Fund account in U. S. Treasury, 1½%, was not approved, but it was voted to invest this amount, together with the \$20,000.00 above approved for investment for the General Fund account"

In commenting upon the report, Dr. Miller stated that his Committee finds the financial situation of the College most satisfactory. He expressed full satisfaction and appreciation of the value of the services of our Investment Counsel. This Counsel has been of constant aid to the Committee, and in their recent survey commended very highly the character of the College investments.

Upon motion by Dr. James Alex. Miller, seconded by Dr. William Gerry Morgan, it was voted that the report of the Finance Committee be accepted and adopted.

At this point in the program, the Washington, D. C., delegation was admitted, in order that it might present its invitation to the College to hold its 1939 Annual Session in Washington.

An invitation to meet in Washington, D. C., in 1939 was extended by Dr. William Gerry Morgan, Secretary-General, by Dr. Wallace M. Yater, Governor for the District of Columbia, by Dr. Thomas Parran, Surgeon General of the U. S. Public Health Service, by Admiral Percival S. Rossiter, Surgeon General of the U. S. Navy and by Dr. Robert U. Patterson, former Surgeon General of the U. S. Army.

DR. CHARLES H. COCKE, Chairman of the Board of Governors: "The Board of Governors, being deeply sensible of, and deeply grateful for the hospitality of the Regents during recent years, instructed me to invite you to be their guest at the next Annual Meeting, on the Sunday evening preceeding the opening of the Session."

Dr. Cocke further reported that there had been the largest attendance by members of the Board of Governors in the history of the College.

President Bradley expressed the thanks of the Regents for the invitation from the Governors, and accepted the invitation on behalf of the Regents.

President Bradley then reported that there had been a special committee, consisting of the President, President-Elect and the First Vice President, appointed during December, 1936, to confer with a committee from the American College of Surgeons on general subjects. Such a meeting was held at St. Louis with Dr. George Crile and Dr. Irvin Abell, representing the American College of Surgeons, Dr. Crile being Chairman of their Board of Regents, and Dr. Abell being the Secretary. Out of the meeting grew no definite recommendations to be made to the Board of Regents of the American College of Physicians. Dr. Bradley, however, recommended that a like committee be appointed during the coming year to continue these conferences.

Dr. Bradley thereupon called upon Dr. Maurice C. Pincoffs to read the statement concerning the withdrawal of the amendments to the Constitution and By-Laws, as authorized at the preceding meeting of the Board of Regents, which Dr. Pincoffs presented as follows:

"It is the feeling of the Regents that the standards for admission to the College should be progressively raised. A change in the By-Laws, making certification by the American Board of Internal Medicine a prerequisite to Associateship, was considered in recent months by the Regents. It was felt, however, that this would at this time constitute too radical an increase in the requirements, and so this proposed amendment has been withdrawn. After further consideration, other proposals for increasing the standards will be submitted to the College.

"Another amendment discontinuing the admission to the College of physicians working in fields allied to Internal Medicine has likewise been withdrawn by the Regents. It is the present feeling of the Regents that the admission of a certain number of Fellows representing these specialties would be desirable. Any application for Fellowship

in this class should be scrutinized with especial care, and should ultimately probably require the certification of each candidate by his own special certifying Board, or, lacking that, its equivalent in professional or scientific achievement."

Upon motion by Dr James Alex Miller, seconded by Dr Walter L Biering, and regularly carried, it was

RESOLVED, that the Board of Regents approve of the above statement

Dr Charles H Cocke, is Chairman of the Board of Governors, again inquired about the matter of alternate Governors. He reported that alternate Governors had been seated at the present meetings by agreement within the Board of Governors.

President Bradley said that he felt there would be no objection to this action until the particular amendment to the By-Laws has been officially adopted.

The Executive Secretary then presented a report on the Associates who were elected at the 1932 Annual Session. The following analysis was presented:

Qualified for Fellowship	70
Deceased	3
Resigned	2
Failed to take up election	1
Dropped	9
	<hr/>
Total candidates elected '32 Session	85

Nine Associates elected at the 1932 Session were automatically dropped for failure to present the requisite credentials for Fellowship within the five-year maximum period, as provided by the By-Laws.

Six Fellows and 5 Associates were by resolution discontinued on the Roster of the College because of delinquency of more than two years' standing.

The Executive Secretary then presented to members of the Board of Regents copies of the pamphlet in which all gifts to the College Library have been recorded, the pamphlet being an index to the College Library of publications by members. A sufficient quantity of these indices have been printed, and were being given to all members interested at this Session.

Mr Loveland then called to the attention of the Board of Regents that a new Directory of the College would be published during the coming summer. He asked for directions in two respects: (1) whether it is the wish of the Board of Regents that the Directory continue to carry the names of Associates, as well as Masters and Fellows, (2) he suggested the appointment of a consulting committee to consider what specialty listings would be approved for record in the Directory.

In the discussion that ensued, it was the consensus of opinion that the Associates should continue to be listed in the Directory, and that a plan should be worked out by which those consulting the Directory would not likely confuse Associates with Fellows.

On motion by Dr James Alex Miller, seconded by Dr Walter L Biering, and regularly carried, it was

RESOLVED, that there shall be appointed a committee of three to act in a consulting capacity in regard to the publication of the new Directory, this committee being delegated power to decide on the manner of listing Associates, and the list of sub-specialties to be recognized.

Adjournment

Attest E R LOVELAND,
Executive Secretary

MINUTES OF THE BOARD OF REGENTS

St Louis, Mo

April 23, 1937

The final meeting of the Board of Regents, during the Twenty-first Annual Session, was held at the Jefferson Hotel, St Louis, April 23, 1937, with President James H Means presiding, Mr E R Loveland acting as secretary, and with the following Regents present

James H Means, *President*,
William J Kerr, *President-Elect*,
David P Barr, *First Vice-President*,
G Gill Richards, *Second Vice-President*,
William Gerry Morgan, *Third Vice-President*,
William D Stroud, *Treasurer*,
Ernest B Bradley,
O H Perry Pepper,
Walter L Biering,
Hugh J Morgan
James E Paulin,
Egerton L Crispin,
James Alex Miller,
Francis M Pottenger,
Charles H Coeke,
Maurice C Pineofts

Upon motion duly seconded and carried, it was RESOLVED to dispense with the reading of the Minutes of the preceding meeting of the Board of Regents

The Chairman recognized Dr John H Musser, of New Orleans, who presented an urgent invitation for the College to hold its 1939 Annual Session in New Orleans

The Chairman also recognized Dr William J Kerr, of San Francisco, who presented a like invitation for the College to hold its 1939 Annual Session in San Francisco

Dr Bradley reported that some of the Cincinnati Fellows of the College had expressed to him the desire to extend an invitation to the College to meet in Cincinnati Dr Bradley stated that he was herewith presenting the invitation from Cincinnati, to consider that City some year in the future He reviewed the general and clinical facilities of Cincinnati for holding the meeting

At this point, the secretary, Mr Loveland, was asked to read the invitation of the City of Cleveland, in the absence of Dr Willard C Stoner, who had been unable to remain for this meeting

Mr Loveland presented the invitation prepared by Dr Stoner for the College to select Cleveland for its 1939 Annual Session He also reported that he had before him telegrams from the Mayor of Cleveland, from the Convention Bureau, from the Dean of Western Reserve University School of Medicine and from the Academy of Medicine of Cleveland, all urging the acceptance of Cleveland for the 1939 Session

Mr Loveland also reported that there was still outstanding an invitation from Memphis for one of the Annual Sessions of the College

The Chairman, Dr Means, then recognized Dr James Alex Miller

DR JAMES ALEX MILLER "I may say that since the last meeting of the Board of Regents, when New York's invitation was first suggested, or offered we have had an expression of medical interest in the College on behalf of very outstanding members of the Medical Profession, and from inquiries which some of us have made, there is no doubt whatever that if we decide to come to New York next year, you are going to have 100 per cent cooperation from all the large medical centers

"Also, from preliminary surveys of the opportunities that will be offered from the standpoint of hotel accommodations, accommodations for the clinical staff, for the round tables, for the exhibits, and all of that part which has to do with the executive side of the Session, it seems as though if we do decide to come to New York next year, and we decide fairly soon, we will be able to get what we consider ideal accommodations.

"So that, on behalf of the Officers of the College, resident in New York, and also on behalf of a large number of others, including the Mayor and others who are interested in New York as a convention center, whose communications I will not take the trouble to read to you, we can offer you a very hearty invitation, and I think we can promise to put on a very good meeting for the College at that time."

At this point, the Chairman recognized Dr M A Shillington, of St Paul, who presented an invitation to the College to select St Paul for its 1939 Annual Session. Dr Shillington discussed in detail the facilities of St Paul and the advantages of holding an Annual Session of the College in that City.

Dr Charles H Cocke, Chairman of the Board of Governors, was called upon for a report of that Board. He stated that at the second meeting of his Board, thirty-nine members had been present, and that they had received the report from the Board of Regents with interest and earnest consideration. The Board of Governors wished to recommend to the Consulting Committee on the Directory that the Associates be listed in the Directory, but in the geographical index be designated as "Associates" and listed immediately under the same States and cities as the Fellows.

The Board of Governors had voted unanimously to recommend to the Committee on Postgraduate Study, through the Board of Regents, that the courses be developed as soon as practicable, and that they should be of a minimum of not less than two, or of a maximum of not more than four weeks' duration.

The Board of Governors also had voted unanimously to recommend to the Board of Regents that the "allied specialties" be retained in the Constitution.

On motion duly seconded and regularly carried, it was

RESOLVED that the report from the Board of Governors be received and recorded.

At this point, the order of business called for the election of the Treasurer and Secretary-General for 1937-38.

On motion by Dr Paullin, seconded by Dr Richards, and unanimously carried, Dr William D Stroud was nominated for reelection as Treasurer. As there were no other nominations, Dr Stroud was declared elected.

Dr William Gerry Morgan "Mr President, I wish to put in a nomination, but before doing so, I want to take this opportunity to express my profound and heartfelt appreciation for the honor extended to me and the courtesies which I have received during my incumbency. My experience during these four years has shown me that it would be very much to the advantage of the College to have a Secretary-General in Philadelphia. There is such a constant exchange of material and matters between the Executive Secretary and the Secretary-General that it would facilitate the carrying on of these business affairs, and it would be a saving to the College from the point of postage and otherwise. Therefore, I take the very greatest pleasure in nominating Dr George Morris Piersol as Secretary-General."

The nomination of Dr Piersol was seconded by Dr Bradley. There were no other nominations and Dr George Morris Piersol was unanimously elected Secretary-General.

The Chairman recognized Dr S Marx White, who entered at this time to second the invitation for the College to select St Paul for its 1939 Session.

President Means then called for the election of an Executive Committee for 1937-38, reading the provisions in the By-Laws governing the same. The President, the President-elect, the Secretary-General and the Treasurer are members of the Executive Committee ex officio. The five additional members formally elected were as follows:

Walter L. Bierring, Des Moines
 Roger I. Lee, Boston
 James Alex. Miller, New York
 Hugh J. Morgan, Nashville
 Maurice C. Pincoffs, Baltimore

President Means then proceeded to the matter of the appointment of committees, reading the personnel of standing committees, the regulations governing same and the names of those whose terms have expired.

The following appointments were made:

COMMITTEE ON ADVERTISEMENTS AND COMMERCIAL EXHIBITS

George Morris Piersol, Chairman, Philadelphia
 William D. Stroud, Philadelphia
 William Gerry Morgan, Washington

COMMITTEE ON THE ANNALS OF INTERNAL MEDICINE

Walter W. Palmer, New York (term expiring 1940)—taking the place of Dr. Egerton L. Crispin, whose term expired. Dr. Means relinquished the Chairmanship and appointed Dr. David P. Barr, already a member of the Committee, to act as Chairman.

COMMITTEE ON FELLOWSHIPS AND AWARDS

James D. Bruce and Egerton L. Crispin appointed in the place of James H. Means and William J. Kerr.

CONSULTING COMMITTEE ON ANNUAL SESSIONS

Appointments automatic—the Committee for 1937–38 shall consist of

James H. Means, Boston, *Chairman*
 James Alex. Miller, New York
 David P. Barr, St. Louis
 Ernest B. Bradley, Lexington

COMMITTEE ON CONSTITUTION AND BY-LAWS

Alfred Stengel (term expiring 1940), reappointed to succeed himself.

COMMITTEE ON CREDENTIALS

George Morris Piersol (term expiring 1940), reappointed to succeed himself from the Board of Regents.

Ernest B. Bradley (term expiring 1938), to fill out the unexpired term of the late Dr. Luther F. Warren.

Dr. Cocke reported that he had reappointed from the Board of Governors, Dr. William B. Breed (term expiring 1940).

COMMITTEE ON FINANCE

Roger I. Lee (term expiring 1940), reappointed to succeed himself.

COMMITTEE ON NOMINATIONS

(President Means announced that he would make his appointments to this Committee in accordance with the By-Laws, within thirty days.)

MINUTES OF THE BOARD OF REGENTS

COMMITTEE ON PUBLIC RELATIONS

Walter L. Biering (term expiring 1941), reappointed to succeed himself
(James H. Means, as President, becomes a member of this Committee, ex officio, succeeding Ernest B. Bradley)

AMERICAN BOARD OF INTERNAL MEDICINE

Representatives appointed by the American College of Physicians included the reappointment of Jonathan C. Meakins (term expiring 1940), and the reappointment of G. Gill Richards (term expiring 1940)

HOUSE COMMITTEE

(The House Committee, consisting of O. H. Perry Pepper, William D. Stroud and James Alex. Miller, had already been reappointed by the Board of Regents at an earlier meeting)

COMMITTEE ON FUTURE POLICY FOR THE DEVELOPMENT OF INTERNAL MEDICINE

(The entire Committee listed below was reappointed)

James Alex. Miller, New York, *Chairman*
Walter L. Biering, Des Moines
Roger I. Lee, Boston
Maurice C. Pincoffs, Baltimore
Francis M. Pottenger, Monrovia

COMMITTEE ON POSTGRADUATE SURVEY

William J. Kerr, San Francisco, *Chairman*
Charles H. Coker, Asheville
Hugh J. Morgan, Nashville

COMMITTEE ON REVOLVING LOAN FUND

Maurice C. Pincoffs, Baltimore, *Chairman*
Roger I. Lee, Boston
Francis M. Pottenger, Monrovia

Upon motion by Dr. W. D. Stroud, seconded by Dr. F. M. Pottenger, and unanimously carried, it was

RESOLVED, that the 1938 Annual Session of the College be held in New York City

Upon motion by Dr. G. Gill Richards, seconded by Dr. Walter L. Biering, and unanimously adopted, it was

RESOLVED, that Dr. James Alex. Miller be appointed General Chairman of the 1938 Annual Session

In responding, Dr. Miller expressed his appreciation both for the selection of New York City and for the confidence expressed in his ability by his appointment as General Chairman. He said everything possible would be done to make the meeting successful. Dr. Miller discussed the matter of the date of the meeting and asked for advice and counsel in all matters from the Board of Regents. He stated that he and the Executive Secretary had already been looking into the facilities of the various hotels in New York, and that they would proceed in accordance with instructions from the Board to designate the headquarters and to select an open date. The opinion had been expressed that a meeting early in March would not be particularly popular, because it breaks up the continuity of winter work for a good many fellows and, perhaps, breaks into the curriculum of the undergraduate teaching in the medical centers. He particularly suggested the week beginning April 3 and the week beginning May 10, as possible appropriate times for the meeting.

Dr James Alex Miller, Chairman of the Finance Committee, expressed the appreciation of the Board for the extraordinary services that the Executive Staff of the College performed, with the large amount of work and extra time devoted to the work by the Executive Secretary and his staff

On motion by Dr Richards, seconded by Dr Crispin, and regularly carried, it was

RESOLVED, that the Finance Committee shall take under advisement increases in salary for the Executive Staff, with power to act

Dr Ernest B Bradley, retiring President at this point took the opportunity to thank the members of the Board of Regents for their cooperation with him during his term as President. He recommended that in the future the President should not have charge of the Morning Lectures and Round Tables, but rather that these should be assigned to the General Chairman because the General Chairman in arranging his Clinics should arrange the entire morning program. He expressed the opinion that both of these additions to the program were well justified, as indicated by the large attendance daily. The Morning Lectures were attended by groups numbering from two hundred to four hundred, and the Round Tables turned out to be exceedingly popular.

Dr James Alex Miller pointed out that in his opinion, it is impossible to make up a program of Morning Lectures independent of the General Sessions. There must be close cooperation between the two, he said, and he recommended that possibly the President and the General Chairman might divide the responsibility jointly.

Dr Bradley pointed out that he and the General Chairman, Dr Barr, had consulted frequently, and had worked out all the program more or less, together. Dr Bradley also pointed out that those who had participated in the last two Annual Sessions are members of the Consulting Committee on Annual Sessions and are available to help at all times the President and General Chairman.

President James H Means forwarded the suggestion that the President take charge of the Morning Lectures, so that they may harmonize with the General Sessions, and that the Chairman take charge of the program of Round Tables.

There was general discussion among the members of the Board concerning the propriety of conducting a program of Morning Lectures, some feeling that such a program is unnecessary and that it may conflict with the attendance at the Clinics.

Dr Bradley pointed out that the entire St. Louis program was worked out around the suggestions of the requests of the members. There are those who prefer to attend Clinics, others who prefer the practical Morning Lectures, and a great host who asked for the addition of the Round Tables. He emphasized the importance of giving the members of the College at large what they personally want on the program, rather than dictating what they should have.

Dr Barr disclosed that he had not been in favor of the Morning Lectures, because he felt that they would greatly interfere with his program of Clinics. However, as the meeting turned out, the Morning Lectures were a great advantage in view of the fact that the meeting had been so much larger than expected, that had it not been for the Morning Lectures to take care of overflows, the Clinics would have been swamped. He expressed the opinion that the Morning Lectures might be highly appropriate in the smaller cities where clinical facilities are limited, but that the program might be abbreviated in larger cities where there are unlimited clinical facilities.

Dr Bradley referred to an editorial written by the late Dr Aldred Scott Warthin, some years ago, in which he recommended that at least one session be devoted to the discussion of general questions. He recommended that this might be considered by the program committee for the following year.

Dr William J Kerr decried the tendency of morning clinics developing into lectures, rather than into practical demonstrations, with the showing of patients. The members at large do not want just an additional set of lectures given as clinics, but they desire real clinics with the demonstration of patients and the discussion of cases. Several endorsed the opin-

ions expressed by Dr Kair and emphasized the importance of arranging programs of real clinics at future meetings. Some expressed the opinion that the St. Louis clinics had been an improvement in this respect over the clinic programs given in some other cities.

Dr James Alex. Miller inquired whether those who attend the Morning Lectures are merely the indolent ones who do not get up in time to reach the clinics, and, if such were the case, whether the Morning Lectures should not be delayed until ten-thirty in the morning, and only give a course for an hour or an hour and a half.

Dr Bradley pointed out that in his opinion men went to the Morning Lectures because they were interested in them, and not because they didn't get up in time to go to the Clinics.

Dr Barr reported that the Clinics, especially at the Barnes Hospital, had been largely oversubscribed, and that as many as two hundred had been turned away from some Clinics because of lack of room to accommodate them. An attempt had been made to engage door-men so that those who had reserved tickets would be assured of admission.

Someone pointed out the necessity of scheduling the Round Tables at the New York Session at such time that those attending the Clinics would be able to get back to the Round Tables on time, so that those attending the Round Tables would not be disturbed by attendants coming in continuously throughout the hour.

Dr Richards pointed out that the most distinguishing feature in the Annual Sessions of the American College of Physicians is the program of clinics. He recommended that where possible clinics should be provided for in such quantities as to accommodate every one who desires to attend.

There was some discussion about holding some of the Round Tables at the medical centers where clinics would be conducted in New York. Dr Miller said that this very likely could be arranged at the Presbyterian Hospital, but that other centers would be sufficiently close to the headquarters to make it possible for attendants to return in time for the Round Tables. He further referred to the very excellent facilities at the Waldorf-Astoria Hotel for many Round Tables, with the additional facilities for luncheons.

Dr Barr recommended that there be a gap of a half hour for transportation between the end of the Clinic program and the beginning of the Round Table program. This had not been so arranged at St. Louis with the result that there had been much difficulty in the attendants getting back for the Round Tables.

Adjournment

Attest E. R. LOVELAND,
Executive Secretary

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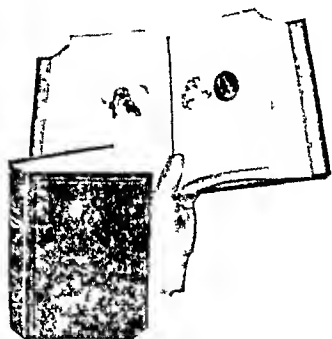
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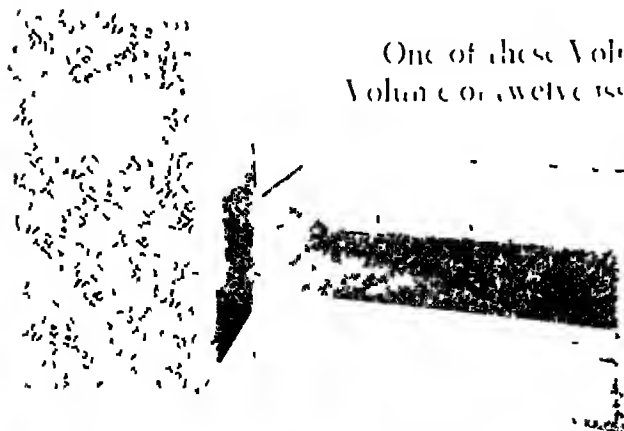
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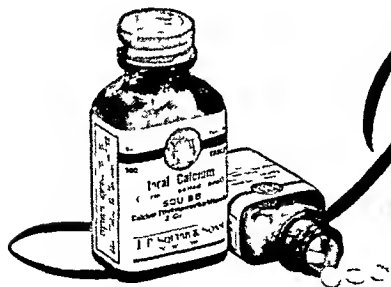
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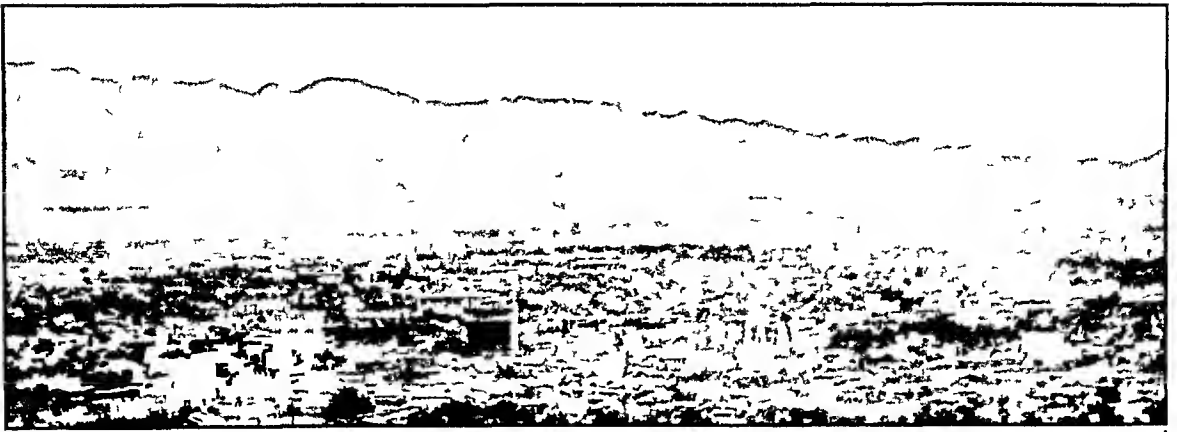
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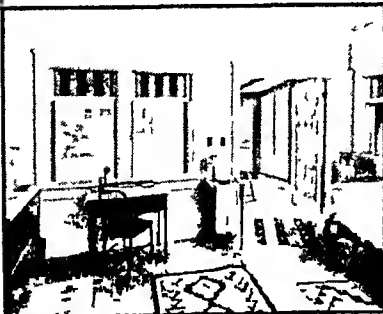
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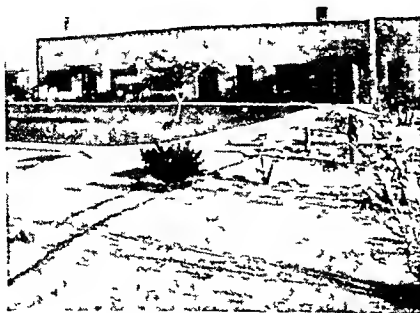


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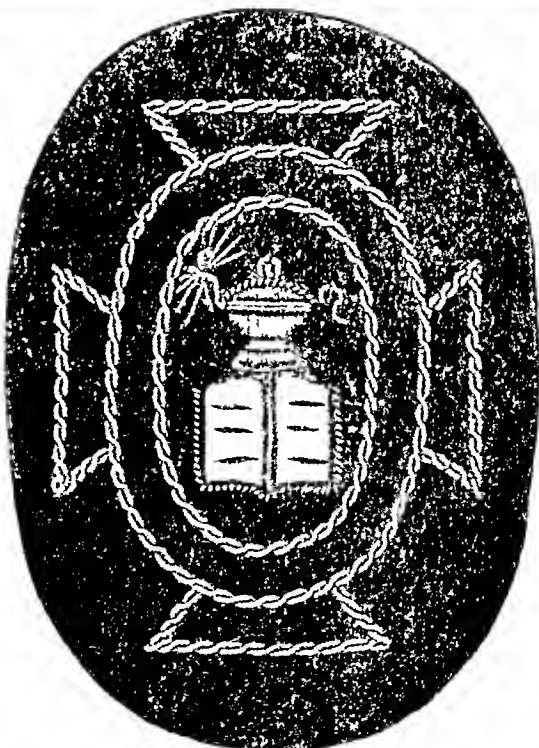
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Place of Publication—Prince and Lemon Sts, Lancaster, Pa

Editorial Office—University Hospital,
Baltimore, Md

Executive Office—4200 Pine Street,
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THE ANNALS OF INTERNAL MEDICINE is published by the American College of Physi-

The contents consist of contributions in the field of internal medicine, editorials, book reviews, and a section devoted to the affairs of the College

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DOE, J. E. What I know about it, Jr. Am Med Assoc, 1931, xcvi, 2006-2008

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American College of Physicians
4200 Pine Street, Philadelphia, Pa

ANNALS OF INTERNAL MEDICINE

PUBLISHED BY

The American College of Physicians

DL 11 (OS, Vol XVI)

AUGUST, 1937

NUMBER 2

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Continued on Inside Back Cover Page

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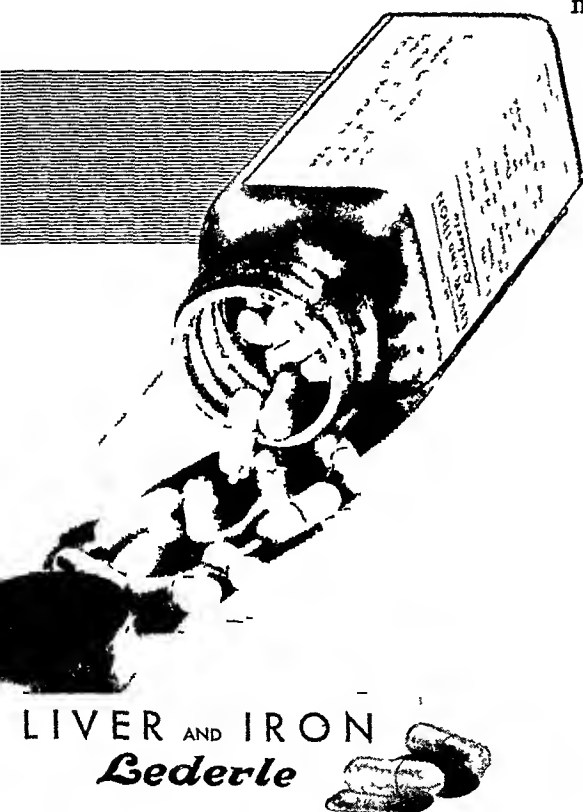
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2 tablespoonfuls vinegar					
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1/2 cup chopped celery	60	1		2	
1/4 cup canned green peas	40	1		4	
1/4 cup cooked carrots cubed	40			4	
Total		11		19	120
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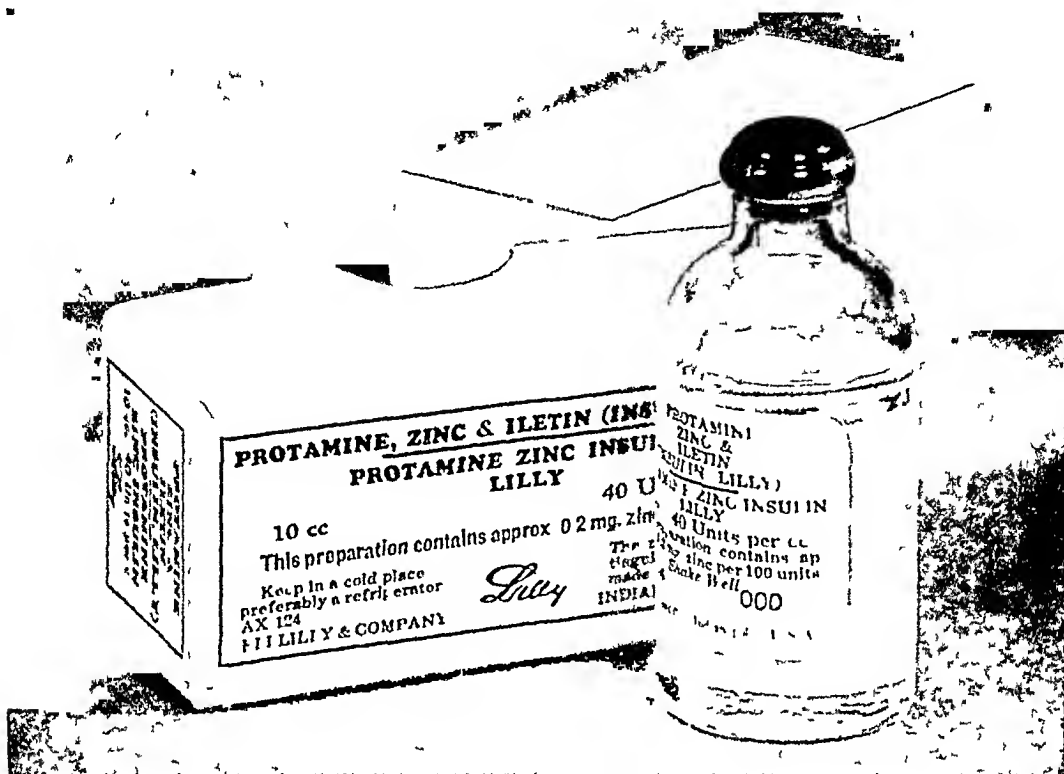
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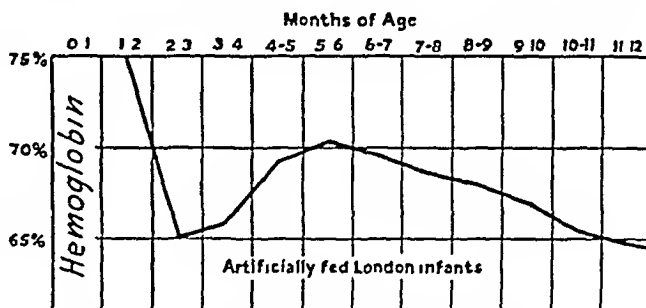


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Nutritional Anemia in Infants

The accompanying chart of the hemoglobin level in the blood of infants is based on more than 1,000 clinical cases studied by Mackay. The sharp drop in hemoglobin during the early months of life has also been reported by a number of other authorities. It is noteworthy that this fall in hemoglobin has been found to parallel closely that of diminishing iron reserve in the infant's liver.

The usual milk formula of infants in early life further contributes to this anemia because milk is notably low in iron. It is now possible, however, to increase significantly the iron intake of bottle-fed infants from birth by feeding Dextrin-Maltose With Vitamin B in the milk formula. After the third month Pablum as the first solid food offers substantial amounts of iron for both breast- and bottle-fed babies.



Reasons for Early Pablum Feedings

1. The iron stored in the infant's liver at birth is rapidly depleted during the first months of life (Mackay,¹ Elvehjem²)
2. During this period the infant's diet contains very little iron—1.44 mg per day from the average bottle formulae of 20 ounces, or possibly 1.7 mg per day from 28 ounces of breast milk (Holt³)

For these reasons, and also because of the low hemoglobin values so frequent among pregnant and nursing mothers (Coons,⁴ Galloway⁵), the pediatric trend is constantly toward the addition of iron-containing foods at an earlier age, as early as the third or fourth month (Blatt,⁶ Glazier,⁷ Lynch⁸)

The Choice of the Iron-Containing Food

1. Many foods reputed to be high in iron actually add very few milligrams to the diet because much of the iron is lost in cooking or because the amount fed is necessarily small or because the food has a high percentage of water. Strained spinach, for instance, contains only 1 to 1.4 mg of iron per 100 gm (Bridges⁹)
2. To be effective, food iron should be in soluble form. Some foods fairly high in total iron are low in soluble iron (Summerfeldt¹⁰)
3. Pablum is high both in total iron (30 mg per 100 gm) and soluble iron (7.8 mg per 100 gm) and can be fed in significant amounts without digestive upsets as early as the third month, before the initial store of iron in the liver is depleted. Pablum also forms an iron-valuable addition to the diet of pregnant and nursing mothers.

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ANNALS OF INTERNAL MEDICINE

VOLUME 11

AUGUST, 1937

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KETONIC AND NON-KETONIC ESTROGENS ~

By W W WESTERFELD and EDWARD A DOISY, *St Louis, Missouri*

INTRODUCTION

ACTIVE experimental work on the internal secretion of the ovary began with the demonstration of Knauer ¹ in 1899 that transplantation of the ovary from its normal site did not produce atrophy of the uterus. Following these experiments many other investigators have made important contributions to our knowledge in this field. Adler,² Fellner,³ Hermann,⁴ Frank ⁵ and others prepared extracts which were active in producing growth of the uterus.

Two other investigations played an important rôle in the development of this field. The first was the introduction (Allen and Doisy ⁶) of the accurate and convenient method of assay by the vaginal smear reaction of rats and mice. The second was the discovery of Aschheim and Zondek ⁷ of the great concentration of estrogenic substances in the urine of pregnant women and mares.

The chemist, supplied with a rapid bioassay procedure and an abundant source of material, lost little time in showing his appreciation. Within the two years following the discovery of Aschheim and Zondek two pure crystalline estrogens were isolated from human pregnancy urine. The isolation in 1929 of the first crystalline estrogen was followed by a deluge of crystalline compounds with estrus producing properties until now some six or seven well characterized compounds have been isolated.

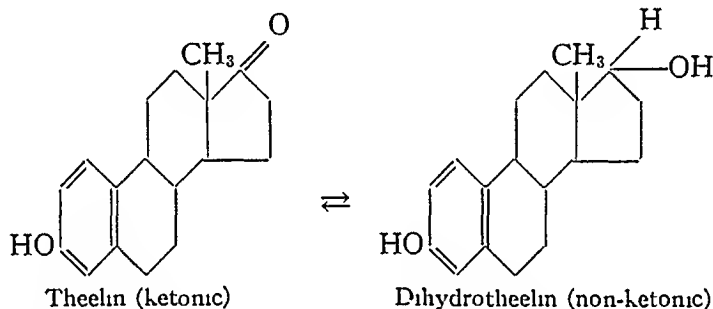
Only two of these estrogens, theelin and theelol, have been obtained from human urine. Although we have examined large quantities of human urine for other estrogens our experiments are thus far unsuccessful. On the other hand, the urine of pregnant mares contains at least six pure estrogens which have been isolated due mainly to the efforts of Girard ⁸ and of Wintersteiner and Schwenk ⁹. Curiously enough in spite of this large number, no theelol has been detected.

With the sole exception of the estriol obtained from human placenta (Browne ¹⁰) no other pure estrogen had been obtained from mammalian

* Read at the St. Louis meeting of the American College of Physicians, April 19, 1937.
From the Biochemistry Department, St. Louis University School of Medicine, St. Louis

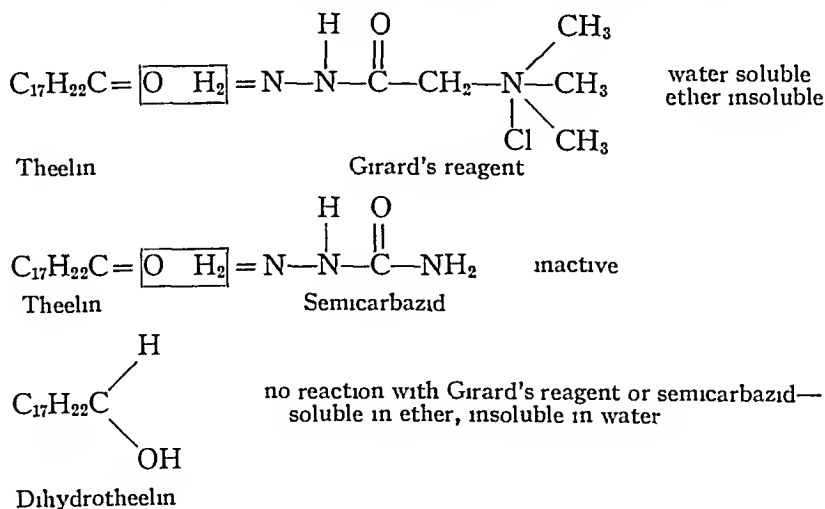
tissues until in 1934 the question of the identity of the follicular hormone attracted our interest. We (MacCorquodale, Thayer and Doisy¹¹) expected to find theelin but instead obtained a reduction product of theelin, dihydrotheelin. Some of our findings may be of interest. About four tons of sow ovaries were extracted and the extract purified. Calculated as dihydrotheelin only about 25 mg were present in the four tons, a relationship of 1 part per 150,000,000. Approximately one half of the activity was recovered in a pure condition and the compound fully characterized. Recently, we have obtained good evidence of the existence of another estrogen in liquor folliculi of sow ovaries.

Chemically, the natural estrogens are closely related compounds which are derivatives of the cyclopentanophenanthrene ring systems. All are phenols and in addition each contains an alcoholic or ketonic radical. In our recent work we have applied methods to the study of the occurrence of the ketonic and non-ketonic estrogens. The formulas illustrate the relationship of these two forms.



Using Girard's¹² reagent which reacts with ketones to render them soluble in water and insoluble in ether it seemed that it might be possible quantitatively to separate the ketones from the alcohols as they occur in organs or in excreta.

Reactions of Theelin with Girard's Reagent and Semicarbazid



EXPERIMENTAL

Studies of mixtures of theelin and dihydrotheelin of known composition enabled us to apply Girard's reagent to quantitative work. Our data (table 1) lead us to believe that the separation is fairly accurate, but that the most likely error is in the possibility of obtaining low values for the ketonic fraction. Furthermore, confirmation of the results for the ketonic fraction can be obtained by treating this fraction with semicarbazid. This treatment causes the loss of at least 98 per cent of the activity of theelin.

TABLE I
Control of Methods

Substance tested	Rat units of non-ketonic recovered	Rat units of ketone recovered
1 0.436 mg theelin (870 R U)	<3	865
2 0.0425 mg dihydrotheelin (720 R U)	700	<5
3 Urine extract containing 300 R U dihydrotheelin plus 180 R U theelin	360	130
After semicarbazid treatment	350	<11
4 Urine extract containing 300 R U dihydrotheelin plus 250 R U theelin	350	210
After semicarbazid treatment	340	—

Having worked out satisfactory methods for the quantitative separation of the ketonic from the non-ketonic estrogen, we investigated two interesting points: 1 the distribution of the two forms in ovaries and placenta, and, 2 the transformations that occur after the administration of pure theelin or dihydrotheelin.

KETONIC ESTROGENS IN TISSUES

Sow ovaries, from which the liquor folliculi and corpora lutea had been removed, were extracted with boiling ethyl alcohol. Purification was effected by methods commonly used in our laboratory. Upon fractionation between ketonic and non-ketonic estrogens it was found that a small but definite quantity of ketonic estrogen is present (table 2). This finding was confirmed by treatment with semicarbazid which destroyed the estrogenic property of the ketone.

TABLE II
Estrogens in Ovaries and Placenta

Tissue	Total rat units	Non-ketonic rat units	Ketonic rat units
Sow ovaries after aspiration of liquor folliculi and removal of corpora lutea	320	300	15
Cow ovaries after removal of corpora lutea	350	350	<5
Human placenta		600	200

Using the same methods, the study of cows' ovaries gave no evidence of the existence of a ketonic form, thereby adding one more item to species differences observed in studies of the follicular hormone

In spite of all of the chemical investigations of human placenta, there is no report of the isolation of any estrogen other than theelin. The extract of 10 placentas was purified. On a per kilo basis, the placenta contained about 800 rat units, of which approximately $\frac{1}{4}$ (200 R U) was ketonic. Since theelin is the ketonic estrogen in human pregnancy urine, probably theelin occurs in placenta. We expect to continue our work on human placenta with the purpose of isolating this ketone in crystalline form.

THE TRANSFORMATION OF ESTROGENS IN THE MONKEY

The development of the methods of separation of estrogens enabled us to study the transformations that occur in the organism. A common biochemical procedure in studying the metabolism of a compound is the administration of enough of the substance under investigation to exceed the destructive capacity of the organism thereby leading to the excretion of the original and intermediate products. The work of Zondek,¹³ of Mazer and Israel¹⁴ and others has shown that a large proportion of estrogens is destroyed or at least disappears and does not appear in the urine as estrus producing compounds. It was found that 3 mg of dihydrotheelin and 6 mg of theelin produced an excretion of sufficient quantities of estrogens for our study.

The disappearance of administered estrogens has led us to speculate on the organs in which destruction or transformation occurs. Since the estrogens exert specific effects in the female genitalia a natural supposition is that the hormones might be altered in those organs. Consequently, we have used for our study a normal adult female, an ovariectomized and an ovariectomized-hysterectomized monkey. It appears from our data in tables 3 and 4 that the destruction as measured by the excretion is not due to either the ovaries or uterus.

Each of the monkeys was injected for six consecutive days with the estrogen dissolved in oil. In the case of dihydrotheelin 0.5 mg was administered daily, in the experiment with theelin each monkey received 1 mg daily. Collection of urines by the use of metabolism cages was started on the day that the injections were begun and continued for ten days. Urines were collected over chloroform and each daily specimen was stored in the refrigerator until the experiment was terminated.

To effect the complete removal of estrogens the combined 10 day specimen was hydrolyzed with hydrochloric acid and extracted with ether. The ether solution was purified in the usual way and the separation of ketonic from non-ketonic estrogens carried out by the procedure already mentioned.

TABLE III

Estrogens Excreted after the Administration of 3 mg Dihydrotheelin

Type of monkey studied	Non-ketones excreted (rat units)		Ketones excreted (rat units)		Ratio of R U non-ketones to ketones	Total excretion calculated as dihydrotheelin	
	Total	After semicarbazid	Total	After semicarbazid		Mg	%
Normal	250	225	200	<11	1 25	0 115	3 8%
Castrate *	160	130	70	<11	2 30	0 045	1 5%
Castrate Hysterectomized	290	250	175	<11	1 60	0 105	3 5%

* Loss of some urine suspected

TABLE IV

Estrogens Excreted after the Administration of 6 mg Theelin

Type of monkey studied	Non-ketones excreted (rat units)		Ketones excreted (rat units)	Ratio of R U non-ketones to ketones	Total excretion calculated as theelin	
	Total	After semicarbazid			Mg	%
Normal	200	175	300	0 67	0 162	2 7%
Castrate	210	200	200	1 00	0 112	1 97%
Castrate Hysterectomized	275	250	600	0 46	0 317	5 3%

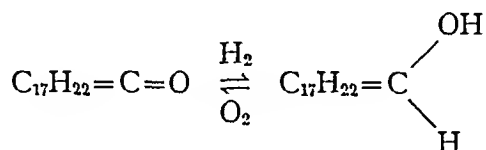
Study of table 3 shows that from 1.5 to 3.8 per cent of the dihydrotheelin was eliminated in the urine. Of these quantities a fair proportion was ketonic, the ratios of non-ketonic to ketonic in terms of rat units being from 1.25 to 2.30.

Turning now to the data obtained following the injection of 6 mg of theelin, we find a slightly larger quantity of estrogen in the urine. In this case from 2 to 5.3 per cent of the theelin was eliminated as estrogenic material, of which a fair percentage was present in a non-ketonic form, presumably dihydrotheelin. A larger proportion of ketone was present in this experiment possibly due to the administration of twice as much estrogen.

We realize that our results with the normal monkey may be complicated due to the possibility of estrogen being formed in its ovaries. However, it is improbable that this animal produced much estrogen since the results on its urine are quite similar to those obtained on ovariectomized monkeys. This similarity of data also leads to the conclusion that the ovaries, uterus and tubes have very little influence on the excretion of administered estro-

gens It seems probable that other organs must play an important rôle in the transformation of estrogens

Our data indicate quite clearly that dihydrotheelin is convertible into a ketonic estrogen and that theelin, a ketone, is converted into a non-ketonic form Although the evidence is not complete our data indicate that the reaction between theelin and dihydrotheelin is reversible in the monkey



SUMMARY

By the application of Girard's reagent to the quantitative separation of ketonic from non-ketonic estrogens the following observations were made

- 1 A ketonic estrogen is present in sow ovaries
- 2 One-fourth of the estrogens in human placenta is ketonic
- 3 The existence of a ketonic estrogen in cow ovaries is doubtful, if present, the concentration is less than 5 units per kilo
- 4 When dihydrotheelin is injected into a normal adult, a castrate, or a castrate-hysterectomized monkey, 30 to 45 per cent of the excreted estrogenic activity is ketonic
- 5 When theelin is injected into a normal adult, a castrate, or a castrate-hysterectomized monkey, 30 to 50 per cent of the excreted estrogenic activity is non-ketonic The evidence indicates that in the monkey the reaction between theelin and dihydrotheelin is reversible and that the ovaries and uterus are not essential for this transformation

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TREATMENT OF DIABETES MELLITUS WITH INSOLUBLE INSULIN COMPOUNDS

II HISTONE-INSULIN

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THROUGHOUT the past two years we have been studying the effect of insoluble insulin compounds in the treatment of human diabetes mellitus. The clinical results obtained with insulin tannate and insulin-zinc compounds have already been reported¹. This communication deals with our clinical trial of the histone-insulin compound discovered and prepared for clinical use by one of us (F B²). This preparation has been found capable of controlling diabetes when used alone. Because of its slow and prolonged action on the blood sugar it is particularly useful in severe types of diabetes in juvenile patients and in elderly cases with cardiovascular complications.

HISTONE

The histones are one of a group of seven simple proteins, the others being the albumins, globulins, glutelins, prolamines, albuminoids and protamines. They are not coagulable by heat and although soluble in water and dilute acids, they are insoluble in ammonia, a feature which is characteristic. In common with the other five simple proteins and in contrast to the protamines they consist of a large number of amino acids. (Table 1)

TABLE I
Chemistry of Protamine and Histone

	Protamine	Histone
Per cent nitrogen	25-30	17
Per cent histidine	Free	5
NH ₄ OH	Soluble	Precipitated
Sulphur	Absent	Present
Per cent amino acids—		
Glycine	0	0.5
Alanine	0	3.5
Leucine	0	11.8
Proline	11	1.5
Phenylalanine	0	2.2
Glutamic acid	0	3.6
Tyrosine	0	5.2
Arginine	87	15.5
Lysine	0	6.9

* Presented at the St. Louis meeting of the American College of Physicians, April 22, 1937.

From the Chemical Laboratories of the Santa Barbara Cottage Hospital and the Sansum Clinic, Santa Barbara, California.

The histone which was used clinically was prepared by the method of Kossel and Kutscher as modified by Bischoff² to reduce the ash content. This ash contains calcium and magnesium. Unknown constituents present in the material used clinically are less than 1 mg per 2500 units of insulin. Thymus glands, C P hydrochloric acid, ammonia water, alcohol and ether are the only substances required in the preparation of the histone.

The histone is added to commercial insulin at the acid side of the isoelectric point of insulin to form a solution. To this is added a disodium phosphate buffer solution which precipitates the histone-insulin on the alkaline side of the insulin isoelectric point. The pH of the solution at the time of injection approximates 6.7. The precipitate is finely divided and readily forms a suspension on shaking. A glass bead has been placed in the sterile, rubber capped vials to facilitate uniform mixture before injection.

Zinc and other metals of the H_2S group are definitely absent from the histone preparations which we have used. The only possible source of zinc would be from the commercial insulin used in the preparation of the combination.

MATERIAL

To date histone-insulin has been used clinically on 30 patients under controlled conditions. These patients have varied in age from 5 to 74 years and present all grades of severity of diabetes mellitus. All were hospitalized during part of the period of observation. Three of these patients have taken histone-insulin for the past three months consecutively. Sporadic observations are available on five additional patients.

TECHNIC OF ADMINISTRATION

Histone-insulin is injected subcutaneously with the ordinary syringe and needle into the same areas of the body as is commercial insulin. In several hundreds of injections only once has any local tissue reaction been noted at the site of injection. This consisted in an ephemeral erythema. No painful subcutaneous lumps have been encountered. Wells³ did not characterize histones as being allergenic. No patient has yet experienced any inconvenience from the injections, even of volumes up to 1.6 c.c. (of a U-50 strength).

When histone-insulin has been used alone to control a patient's diabetes one dose in 24 hours has usually sufficed. This dose is given either one-half hour before or immediately after breakfast. A few patients have required two doses in 24 hours. They have received three-quarters of the total dose after breakfast and one-quarter immediately before supper. Some patients have required a small dose of commercial insulin together with their daily dose of histone-insulin. This has been injected at the same time as the new preparation but with a separate syringe and into a different area of the body.

We recommend that the solution of histone-insulin be kept cool and that

it be shaken vigorously prior to each injection to insure uniform suspension of the insoluble insulin throughout the solution. The preparation used has been reasonably stable.

RESULTS

The observations of Bischoff² that histone delays the absorption and prolongs the hypoglycemic action of commercial insulin have been confirmed in man. Figure 1 shows this effect. Under identical experimental conditions this diabetic patient's blood sugar level remained low for a longer period of time after a single injection of histone-insulin than after regular insulin.

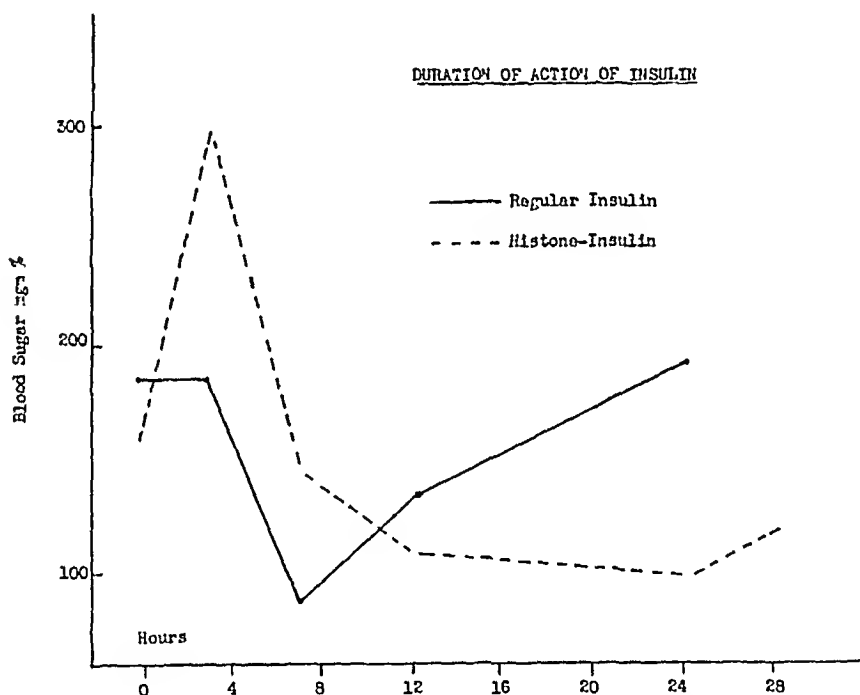


FIG. 1. M. B. A comparative study of the duration of action of regular insulin and histone-insulin in a diabetic male aged 24. On each test day the patient remained at bed rest. Forty units of insulin were given. One-half hour later he ate a breakfast containing C 97, P 27, F 44 and then fasted for the remainder of the test period. Evidence is presented that histone-insulin is absorbed more slowly, but acts over a much longer period than regular insulin.

In another group of experiments the physiologic effects of single doses of commercial insulin, protamine-insulin (zinc)⁴ and histone-insulin were compared on the same patient. The general plan of the experiments was as follows. Each subject ate the same food each test day at the same hour and either remained at bed rest or exercised uniformly. Each test day was separated from the others by a rest period of at least 24 hours. This was felt to be especially essential between the days on which the insoluble compounds were given in order to avoid any accumulative effect. Under the conditions

of the experiments where food was taken at regular intervals the blood sugar level reached its lowest point after a single injection of commercial insulin in four to four and a half hours, and after about ten hours had returned to the fasting level. In the case of both protamine-insulin (zinc) and histone-insulin the lowest point was reached between 14 and 24 hours after the injection.

Table 2 records the effect observed in a diabetic male aged 27. Food was served six times during the day, at 7 00 and 10 00 a m, 12 00 m, 3 00, 6 00 and 8 00 p m as indicated. One half hour before breakfast 45 units of insulin were given subcutaneously. Blood sugar levels were determined before the insulin was given and at three, five, seven and a half, eleven and a half, 15 and 24 hours thereafter. Urine was collected separately from 6 30 a m to 9 00 p m and from 9 00 p m to 7 00 a m the following morning. On the test day when regular insulin was given there

TABLE II

Time	Food			Blood Sugar (mg %)	Urine Sugar (gm)	Blood Sugar (mg %)	Urine Sugar (gm)	Blood Sugar (mg %)	Urine Sugar (gm)
	C	P	F						
6 30 a m				160		158		156	
7 00	48	28	23	Insulin (45-U)		Protamine (45-U)		Histone (45-U)	
9 30				84		244		268	
10 00	10	0	0						
11 30				54		188		192	
12 00 m	47	28	23						
2 00 p m				150		190		174	
3 00	15	2	0						
6 00				240		124		154	
6 00	42	29	26						
8 00				206	8.9	78	0	120	15.3
7 00 a m						100	3	170	0

was no postprandial rise in the blood sugar after breakfast. The blood sugar reached its lowest level five hours after the injection, after which it rose. On both days when the insoluble insulin compounds were given there was a definite postprandial rise after breakfast with a subsequent gradual fall even though the patient continued to eat at the usual times. In the case of protamine-insulin (zinc) this secondary fall was more rapid than with histone-insulin. This difference was probably due to difference in the rate of absorption of the two compounds. Since the subject's blood sugar remained higher for a longer period of time after histone-insulin than after protamine-insulin (zinc), it was to be expected that a greater amount of sugar would be found in the first 12 hour urine specimen on this day. The lowest level of the blood sugar after both of the insoluble compounds was not reached until 15 hours after their injection.

Table 3 records another experiment of the type just described in a diabetic woman aged 53. In this case again the lowest level of the blood sugar after commercial insulin was reached five hours after the injection. After protamine-insulin (zinc) the blood sugar rose after breakfast to fall gradually, reaching its lowest level 24 hours later. After histone-insulin the post-breakfast rise did not occur, presumably because in this instance some free insulin was present in the mixture injected. The smaller amount of sugar present in the night collection of urine noted on each test day when the insoluble-insulin compounds were given suggests continued action, that is absorption of the compound, during the night.

TABLE III

Time	Food			Blood Sugar (mg %)	Urine Sugar (gm)	Blood Sugar (mg %)	Urine Sugar (gm)	Blood Sugar (mg %)	Urine Sugar (gm)
	C	P	F						
6 30 a m				46		76		52	
7 00	56	21	33	Insulin (40-U)		Protamine (40-U)		Histone (40-U)	
11 30				52		276		124	
12 00 m	42	24	27						
5 00 p m				252		248		180	
6 00	59	40	24						
9 00	18	2	0						
10 00				412	14.6	332	17.6	344	24.5
7 00 a m				300	88.4	192	18.2	230	16.3

Table 4 records another similar experiment in a diabetic male aged 74. Here again the delayed absorption and prolonged hypoglycemic action of the insoluble-insulin compounds as contrasted to regular insulin is apparent. As in the preceding two experiments the subject's blood sugar level 24 hours after a single injection was not quite so low after histone-insulin as after protamine-insulin (zinc).

TABLE IV

Time	Food			Blood Sugar (mg %)	Urine Sugar (gm)	Blood Sugar (mg %)	Urine Sugar (gm)	Blood Sugar (mg %)	Urine Sugar (gm)
	C	P	F						
7 00 a m				180		196		202	
7 30				Insulin (30-U)		Histone (30-U)		Protamine (30-U)	
8 00	56	14	18						
11 30				88		228		296	
12 00 m	42	36	29						
5 00 p m				166		202		222	
6 00	53	28	29						
8 30	18	7	8						
10 00				320	0	346	Trace	276	5.8
7 00 a m				216	4.5	178	Trace	124	0

In all our experiments of this type some action on the blood sugar has been noted 24 hours or more after a single injection of the insoluble compounds. Although individual patients have shown some variation, protamine-insulin (zinc) and histone-insulin have, in general, behaved similarly.

Prior to using histone-insulin the 30 patients upon whom we have sufficient data required 2.7 average injections of commercial insulin daily, while on the new compound 1.2 average injections have sufficed to maintain a comparable degree of control. Various patients have received histone-insulin from a few days to three months continuously. Certain patients have received it intermittently over a year. We have studied principally a group of severe cases, many of them children, because it is obvious that in a high-dosage case requiring multiple injections daily a slow acting insulin would be most useful. Furthermore such cases have been the ones most available to us for such study. The ensuing protocols will show that in addition to reducing the numbers of injections required daily, the histone-insulin has reduced the fluctuations in the patients' blood sugar levels from one part of the day to another. In certain mild cases the effect of a single dose has apparently lasted throughout 48 hours. Recently we have carried several patients through both major and minor surgery by giving them daily injections of histone-insulin supplemented by small amounts of commercial insulin.

Histone-insulin and protamine-insulin (zinc) have had the same relative effect on this group of patients. Certain patients have been changed from one to the other easily with only minor readjustments. Some who have not been satisfactorily controlled with one of these new compounds have been with the other. The principal difference noted thus far in their clinical effect has been in the frequency of hypoglycemic reactions the morning of the day following the injection. Such reactions have been somewhat more frequent with protamine-insulin (zinc) than with histone-insulin. The recent review of the literature on protamine-insulin by Wilder⁵ makes further discussion of this preparation unnecessary.

HYPOGLYCEMIC REACTIONS

In appropriate dosage histone-insulin is capable of inducing characteristic hypoglycemic reactions. These usually appear 24 hours after a single injection and coincide with the peak of the depression of the blood sugar. Since the histone-insulin is injected just before or after breakfast, reactions have usually occurred at a corresponding time the ensuing morning.

The mildness of somatic manifestations is noteworthy. Sweating and trembling have been seen rarely. Drowsiness, headache and dizziness are the principal symptoms. Children have, on occasion, been hard to awaken and when finally awake have complained only of headache. We have occasionally seen children who presented no external manifestation of any kind.

and who seemed to be sleeping naturally, at a time when their blood sugar was at shock level.

Relief of hypoglycemic shock has been accomplished in the same manner as after commercial insulin. This difference, however, is worthy of note. Whereas a single dose of readily available carbohydrate usually suffices in the case of regular insulin, repeated doses may be required after histone-insulin, due to late and continued absorption. This phenomenon has been seen in hypoglycemic shock produced by other insoluble insulin compounds.

COMMENT

In this study we have been concerned primarily with determining the role of histone-insulin in the treatment of human diabetes mellitus. Its ability to replace regular insulin as an agent in controlling diabetes has been demonstrated. Considerable individual variation has been noted among the patients studied. In the majority an adequate degree of control has been attained with one dose each 24 hours. Some cases which could not be controlled on one dose have been controlled on two doses. A few others could not be adequately controlled with any practical dosage scheme; these patients have discontinued taking histone-insulin and have resumed regular insulin. In every case studied we have tried to effect control of glycosuria with one dose in 24 hours, or a combined dose of new and regular insulin taken simultaneously. When this has not been possible patients, as a rule, have preferred to return to two (in some cases even three) injections of regular insulin than to continue with the same number of injections of the new preparation.

A control group of patients comparable in number and severity of diabetes to those receiving histone-insulin have been given protamine-insulin (zinc). Our clinical impression at present is that the two groups have behaved quite similarly. Histone-insulin and protamine-insulin (zinc) each have yielded good results in some patients and not in others. They both delay the absorption of insulin. The same patient can be controlled with either preparation and changed from one to the other with only minor adjustments of unitage. Thus far three patients have experienced distressing local reactions at the site of injection of protamine-insulin (zinc), sufficient to warrant the discontinuance of the preparation. None such have been encountered with histone-insulin. Some patients whose diabetes could not be controlled with one dose in 24 hours of one preparation have been controlled satisfactorily when changed to the other.

Our experience with histone-insulin to date has been too limited to warrant any statement concerning the glucose value of one unit of the new insulin compared to that of the old. Some patients in this group have required fewer total units of histone-insulin than of regular insulin on the same diet, the majority have required about the same number and some have required more.

Our records show considerable daily variation in the amount of glycosuria and the level of the blood sugar in those patients whose blood sugar on regular insulin rises during the night. Since the action of histone-insulin is comparable to that of regular insulin² when injected intravenously we have assumed that these irregular variations are due to variable absorption on different days. This difficulty is common to all of the insoluble insulin compounds with which we have worked.

PROTOCOLS

Case 1 J. G., a male, aged 37, has had diabetes for 15 years and angina pectoris for three years. He has been under continuous observation since May 1934. During this period he has never been consistently sugar free, his insulin has been administered in four doses, varying between 66 and 80 units. Normal fasting blood sugar levels have only been obtained when insulin has been given during the preceding night. Before starting the histone experiment this patient had seldom been free of precordial pain on effort for more than 24 hours at a time between 1933 and 1936. Electrocardiograms taken at various intervals have shown a high take-off and rounding of ST₁ and ₂ and depression of T₁ below the isoelectric line. The blood pressure has fluctuated between 140 to 150 systolic and 90 to 100 diastolic. It has been demonstrated that this patient would experience anginal pains whenever his blood sugar fell below 100 or rose above 300 mg per cent. Attacks have been induced at will by inducing fluctuations in his blood sugar and relieved without the aid of vasodilators by restoring the blood sugar to normal.

Table 5 shows that this patient was gradually changed from commercial insulin to histone-insulin. It has sufficed to control his diabetes. One dose per day has replaced four of commercial insulin and effected a comparable degree of control. The number of units of histone now taken daily at one injection approximates those formerly distributed in four. In spite of large volumes of histone-insulin having

TABLE V

Date	Insulin Units			Urine	Blood Sugar	
	a m	m	p m		a m	p m
5-13-34		40	13	25	13.8	
5-15-34	4	30	13	18	+	325
3-11-36	7	38	13	18	18.0	
3-14-36	10	38	13	18	+	
11-24-36		23		18		
		5		10	62.3	344
11-30-36		23		13	45.6	332
		23				270
12-14-36		51		10	5.0	226
1-7-37		56		10	52.0	238
1-21-37		55		10	5.0	
2-10-37		70			5.0	
2-17-37		70			20.0	
3-1-37		75			18.0	280
3-22-37		75			—	124

Diet = C 172, P 83, F 86

Weight = 143-145 lbs

Figures in boldface type indicate Histone

been injected over several months' time no local or systemic reactions have been encountered. The only clinical manifestation of hypoglycemic shock has been headache and dizziness. Since taking histone-insulin this patient has not experienced anginal pain at any time (now over two months), in spite of the fact that his blood sugar level has occasionally attained that known previously to induce an attack. A recent electrocardiogram has been reported to be negative.

Case 2 P R, a boy, aged 14, has had diabetes for five years and has been under continuous observation during this time. On a maintenance diet his 24 hour urine specimens have usually been sugar free. His daily insulin requirement has been about 57 units, given in four doses, for the past three years.

This patient has been changed over to histone-insulin. As shown in table 6 it has sufficed to control his diabetes satisfactorily when injected once daily. Ten to 20 per cent more units per day have been necessary than formerly. The only clinical manifestation of hypoglycemia has been headache. No local reactions at the site of injection have been noted.

The horizontal divisions of table 6 indicate separate periods of hospitalization. The final one (3-26-37) followed an attack of scabies. Loss of carbohydrate toler-

TABLE VI

Date	Insulin Units			Urine	Blood Sugar	
	a m	m	p m		a m	p m
7-30-36	10	18	12	15	+	166
11-15-36		18		15		
		12		8	40.5	44.0
11-21-36		18		15		320
		34		23	Trace	
11-28-36		61			71.7	284
12- 5-36		61				88
12-12-36		62		-		332
12-18-36		56		+		
12-27-36		56		-		182
12-28-36		56		29.6		196
12-29-36		56		-		246
					308	
1-16-37		62		-		
2- 7-36		66		+		
2-19-37		70		-		
3-26-37		63			37.8	408
						360

Diet = C 208, P 84, F 100

Weight = 96.5-102.3 lbs

Figures in **boldface type** indicate Histone

ance during infections is not prevented by using the new insoluble insulin compounds. This observation has been amply confirmed during the recent epidemic of upper respiratory infections.

This patient has received the largest volume of the histone-insulin preparation. While taking it he has gained in weight, felt well, and exhibited no untoward local or systemic effects.

Case 3 B A, a diabetic girl, aged 5 years, was admitted to the hospital in diabetic ketosis. One hundred fifty units of insulin were given during the first 24 hours. After recovery from ketosis the patient was controlled on commercial insulin.

Table 7 shows how this patient was changed over to histone-insulin. One month later a smaller total number of units sufficed to control her diabetes than on commercial insulin. She had gained 2 kg in weight during the period of observation.

TABLE VII

Date	Insulin Units			Urine	Blood Sugar	
	a m	m	p m		a m	p m
2-18-37	15	10	15	7 7	274	76
2-21-37	15	10	15	+		
2-22-37	32		8	—	236	
2-25-37	35		5	—	103	134
3- 7-37	40			Trace	108	
3-17-37	30			2 6		
3-21-37	25			—	354	

Diet = C 145, P 70, F 37, Cal 1193

Weight = 13-15 kg

Figures in **boldface type** indicate Histone

Once while receiving 40 units of histone-insulin this child went into hypoglycemic shock under conditions which may well occur in other patients on home management. She awoke one morning feeling queerly. Her mother, failing to recognize any unusual behavior, gave the usual dose of histone-insulin a few minutes before breakfast as customary. Before breakfast could be eaten the child was unconscious. When readmitted to the hospital the child exhibited an interesting wave-like response to treatment. For a while after the administration of glucose she would arouse, appear normal, talk rationally, drink orange juice, and then sink back into a stupor. This phenomenon continued for 36 hours, indicating a delayed absorption of the histone-insulin. Recovery was complete with no demonstrable ill effects.

Case 4 S. H., a man, aged 74 years, has had diabetes 18 years. Before using histone-insulin there had been no apparent change in his carbohydrate tolerance for many weeks, and the usual insulin requirement was about 50 units. Throughout the three different periods when he received histone-insulin he was confined to bed on account of vascular changes in the extremities. On each trial ranging from two to four weeks one dose of histone-insulin per day controlled his diabetes. Table 8 gives a synopsis of these three different experimental periods.

TABLE VIII

Date	Insulin Units			Urine	Blood Sugar	C	Diet P	F
	a m	m	p m					
1-28-36	31	11	11	—		139	80	69
2- 4-36	27			5 5	196			
2-11-36	40			—	242			
6- 4-36	30		15	—	220	240	77	59
6-14-36	32		14	7 6	202			
6-21-36	30			Trace	204			
7- 3-36	35			—	220			
3-21-37	10	10	10	—		231	82	86
3- 8-37	35			—	154			
3-15-37	35			—	150			

Figures in **boldface type** indicate Histone

SUMMARY

Histone-insulin is capable of controlling human diabetes mellitus when used alone. Its action on the blood sugar is more delayed and prolonged

than that of commercial insulin. No local or systemic reactions have been noted even with injection of a large volume or over long periods of time. In a group of 30 patients an average of 2.7 injections of commercial insulin per day has been reduced to an average of 1.2 injections of histone-insulin.

We are indebted to Mr W R Dickinson of Hope Ranch Park, Santa Barbara, for a grant to cover the preparation of the histone used in this study and to Eli Lilly and Company for a generous supply of insulin.

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ACACIA THERAPY IN NEPHROTIC EDEMA

By MICHAEL J. LEPORE,[†] *Bronx, New York*

DURING the past decade evidence has accumulated from many quarters lending support to the physico-chemical concept of edema formation advanced originally by Starling¹ in 1895. The basis of this theory is that capillary pressure and serum colloid osmotic pressure are opposing forces, the balance between which determines the direction of movement of fluid and of the crystalloidal constituents of the blood across the capillary wall. In view of the numerous excellent papers on the subject, it is needless to review the evidence establishing the validity of the Starling concept in explaining the mechanism of production of nephrotic edema. The lowering in serum albumin concentration and hence in serum colloid osmotic pressure, seen in nephrosis, nutritional edema and similar states is, according to the Starling theory, the major factor determining the incidence of edema in these conditions.

Rational attempts to remove nephrotic edema have, therefore, been aimed at raising the serum colloid osmotic pressure. Transfusions of whole blood, serum or plasma have been used. High protein diets have been given in an attempt to raise serum protein levels by stimulating regeneration of protein. Artificial colloidal substitutes for serum proteins have been proposed, gum acacia being the most popular. Hartman and associates² reported favorably on the use of gum acacia in the treatment of nephrosis in children. In five of six cases, they found that when other measures had failed, the intravenous injection of acacia resulted in the initiation of diuresis. They asserted that the aim of acacia therapy is to raise the serum colloid osmotic pressure to a level of about 17 cm. of water, and in this way to reverse the process of transudation so that absorption of edema fluid is favored. Failures they thought were due to insufficient dosage of acacia. They advocated giving doses of one gram of acacia per kilogram of ideal body weight in the form of a 15 per cent solution.

In 1935, Dick and associates³ recorded discouraging experiences with acacia in the management of nephrotic edema, reporting that acacia was often ineffective in causing diuresis, and that a fall in serum protein concentration and a progressive anemia followed its use. They especially stressed the fact that the decrease in serum protein concentration was of such magnitude as to negate any rise in colloid osmotic pressure produced by the presence of acacia in the serum, the net result being appreciable decreases in the calculated serum colloid osmotic pressure. They reported furthermore

* Received for publication February 8, 1937.

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that following its intravenous injection acacia could be demonstrated in appreciable concentrations in pleural and peritoneal fluids of their patients. Moreover, while the first course of acacia injections was often effective in relieving edema, subsequent injections proved ineffective. Inspection of their protocols reveals that they used adequate amounts of acacia, for relatively massive dosage was employed.

In support of their clinical observations, Dick and associates reported several experiments on dogs. Four dogs were given acacia intravenously, following which the serum protein concentrations of all four animals decreased considerably. With cessation of the acacia injections, the serum proteins returned to normal. There was a distinct tendency in their experiments for both albumin and globulin fractions to vary in the same proportion. The possibility that these results were dilution effects was dismissed by them without the presentation of adequate evidence in support of their interpretation. They concluded that "the use of acacia intravenously in patients with nephrosis was not found of value and was associated with undesirable results."

It is the purpose of this communication to report four instances of nephrotic edema in adults treated with acacia. Certain of the phenomena reported by Dick and associates³ were encountered in these cases, but in the light of actual measurements of the plasma volume, it has been possible to interpret them differently. Two cases (Case 3, M. W., and Case 4, Z. R.) fulfilled the classical requirements for the diagnosis of so-called lipid nephrosis. The other two were definitely cases of chronic active glomerulonephritis in the nephrotic stage.

METHODS

The plasma protein analyses were done by the method of Howe.⁴ The plasma volume measurements in the first three cases were made with the method of Rowntree and associates⁵ as modified by Whipple and associates.⁶ There are certain objections to this method which have been considered in some detail in another report.⁷ However, experience with an improved technic⁷ confirms the general trend of the observations made with the older method and, furthermore, the magnitude of most of the changes to be reported is well beyond the errors inherent in the older method. It has been explained elsewhere⁷ that values for plasma or serum volume obtained by the dye method are not absolutely accurate for they include a small volume of lymph. For this reason, in the present report, emphasis has been placed on the *changes* in serum or plasma volume occurring in the same patient rather than upon the actual values obtained.

Determinations of plasma volume were done on patients who had been fasting for three or more hours and were lying flat in bed. In Case 4, the serum volume measurements were made with the improved method.⁷

Acacia in saline (Lilly) was given in the concentrations stated below. On one occasion acacia without saline was used.

RESULTS

Case 1 V B, white, male, aged 16 years

History Admitted to Duke Hospital on October 13, 1934 complaining of "swelling of the face, ankles, and stomach" of one month's duration. The onset of illness was referred to a "cold" which came on shortly after wading in cold water while swimming. Swelling of the ankles and puffiness of the eyelids were noted on the day following the onset of the cold. The urine, examined on the fifth day of illness by his doctor, boiled solid. He was placed on a low protein diet with fluids restricted and was given magnesium sulphate by mouth. The edema at first diminished but soon recurred and during the week prior to admission had become progressively worse.

Physical Examination Blood pressure, 144 mm of Hg systolic and 110 diastolic. Marked edema of the eyelids is present. There is considerable pre-sacral and pre-tibial pitting edema. Signs of bilateral pleural fluid and of moderate ascites are elicited. The optic fundi show no exudate or papilledema. The tonsils are considerably enlarged and appear chronically infected. No evidence of cardiac failure is present.

Urine Specific gravity 1.035, dark brown, albumin four plus. Microscopic 10 to 12 red blood cells per high power field. Occasional granular cast.

Blood Hemoglobin 16 grams per 100 c.c. Red blood cells 5,570,000 per cu. mm. Blood non-protein nitrogen 34 mg. per cent. Total plasma proteins 3.54 gm. per 100 c.c., plasma albumin 0.67 gm. per 100 c.c., plasma globulin 2.87 gm. per 100 c.c., cholesterol 375 mg. per 100 c.c. Wassermann and Kahn reactions negative.

Kidney function tests Phenol red excretion, 65 per cent excreted in two hours (October 14). Urea clearance, 145 per cent of normal, October 16, 1934 and 95 per cent of normal, October 22, 1934.

Basal metabolic rate minus 27 per cent (October 16, 1934).

Therapy The patient was placed on a high protein, salt-free diet and was kept in bed. The edema remained unchanged. On October 20, 1934, he was given intravenously 45 grams of acacia in saline as a 15 per cent solution. At the end of the infusion, slight urticaria appeared and the proximal phalangeal joint of the right index finger appeared tense and swollen. No febrile reaction occurred. The urticaria and joint swelling subsided after the injection of a total of 0.6 c.c. of a 1-1000 solution of adrenalin. This injection of acacia was followed by an almost immediate and persistent large diuresis. Another 30 grams of acacia in saline as a 15 per cent solution were given on October 22, 1934. The further sequence of events is illustrated in figure 1. It is there seen that after the injection of acacia the plasma volume rose markedly and the plasma protein concentration and cell volume fell, presumably as a result of hemodilution. Diuresis continued as shown. This patient was followed at monthly intervals for another six months and during this time remained practically free from edema on an active regime despite the persistence of marked albuminuria and a low serum albumin concentration. Clinically demonstrable hepatic enlargement was at no time present.

Case 2 D J, colored male, aged 26

History Admitted April 9, 1935 with the complaint of "swelling of the body" of two months' duration. His illness began two months before when he first noted the insidious onset of puffiness of the eyelids and ankles. Smoky urine was also noted at this time. He kept on with his usual activities and the edema soon became generalized. Five weeks after the onset of his initial symptoms, he consulted a

doctor who told him that he had kidney trouble and prescribed a meat-free diet with limited salt. Progressively increasing edema led him to enter the hospital.

The past history reveals the fact that he has had occasional attacks of sore throat. However, he does not remember having had a sore throat with the onset of the present illness. He had a chancre 10 years ago for which he received no anti-luetic therapy.

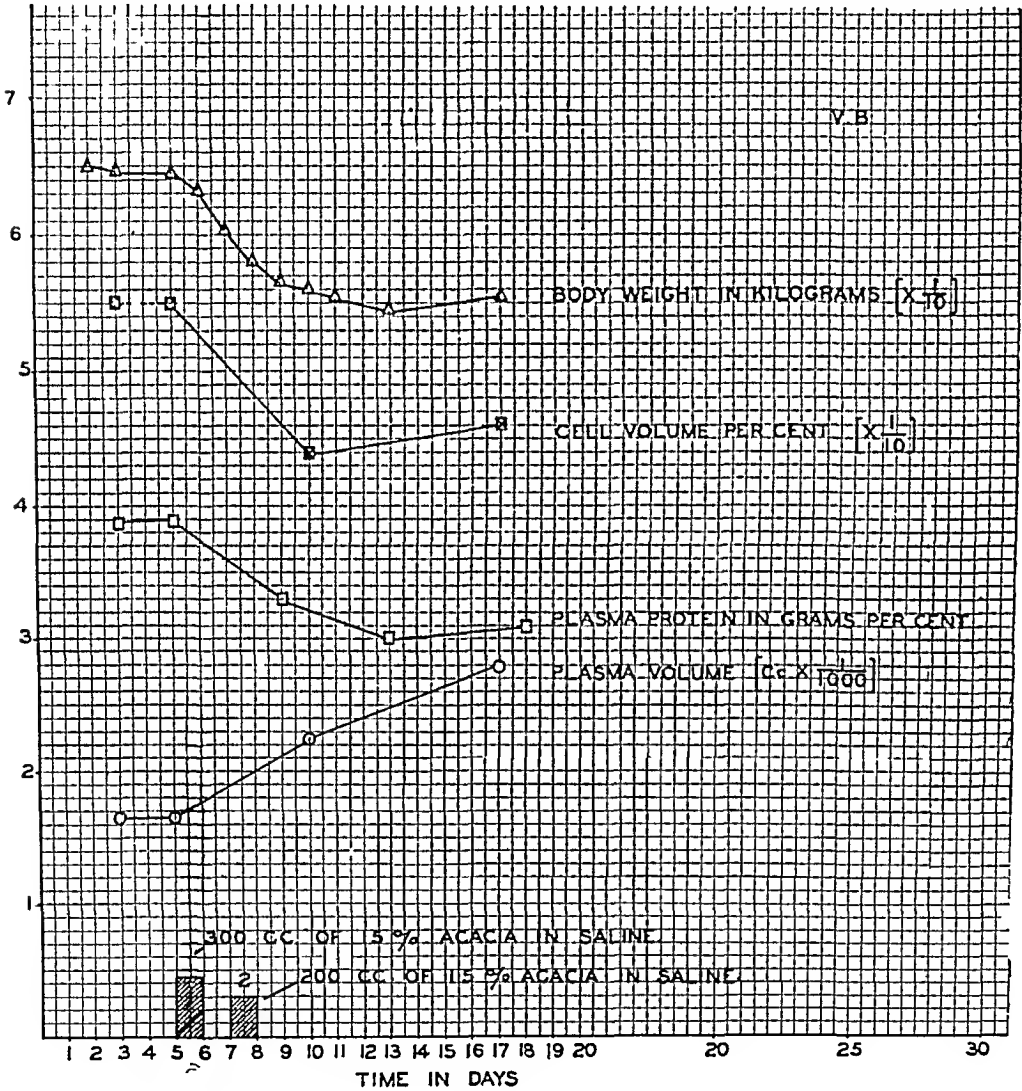


FIG 1

Physical Examination Blood pressure, 186 mm of Hg systolic and 90 diastolic. There is considerable edema of the face and hands. A moderate amount of ascites, and pre-tibial and pre-sacral soft, pitting edema are present. The tonsils are moderately enlarged and seem chronically infected. The heart is moderately enlarged to the left and the sounds are forceful. The liver is not palpable. The fundi oculi show slight bilateral papilledema. No exudates are seen.

Urine Reddish brown, specific gravity 1.016, albumin four plus. Microscopic: Many red blood cells, numerous leukocytes, many coarse granular and hyaline casts.

Blood Hemoglobin 13.6 gm per 100 cc Red blood cells 3,880,000 per cu mm
 Blood non-protein nitrogen 33 mg per cent Total plasma proteins 4.27 gm per 100 cc
 Plasma albumin 1.44 gm per 100 cc Plasma globulin 2.83 gm per 100 cc
 Cholesterol 911 mg per cent Wassermann and Kahn reactions four plus

Kidney function tests Phenol red excretion 65 per cent in two hours Urea clearance, 51 per cent of normal April 16 and 46 per cent of normal May 8

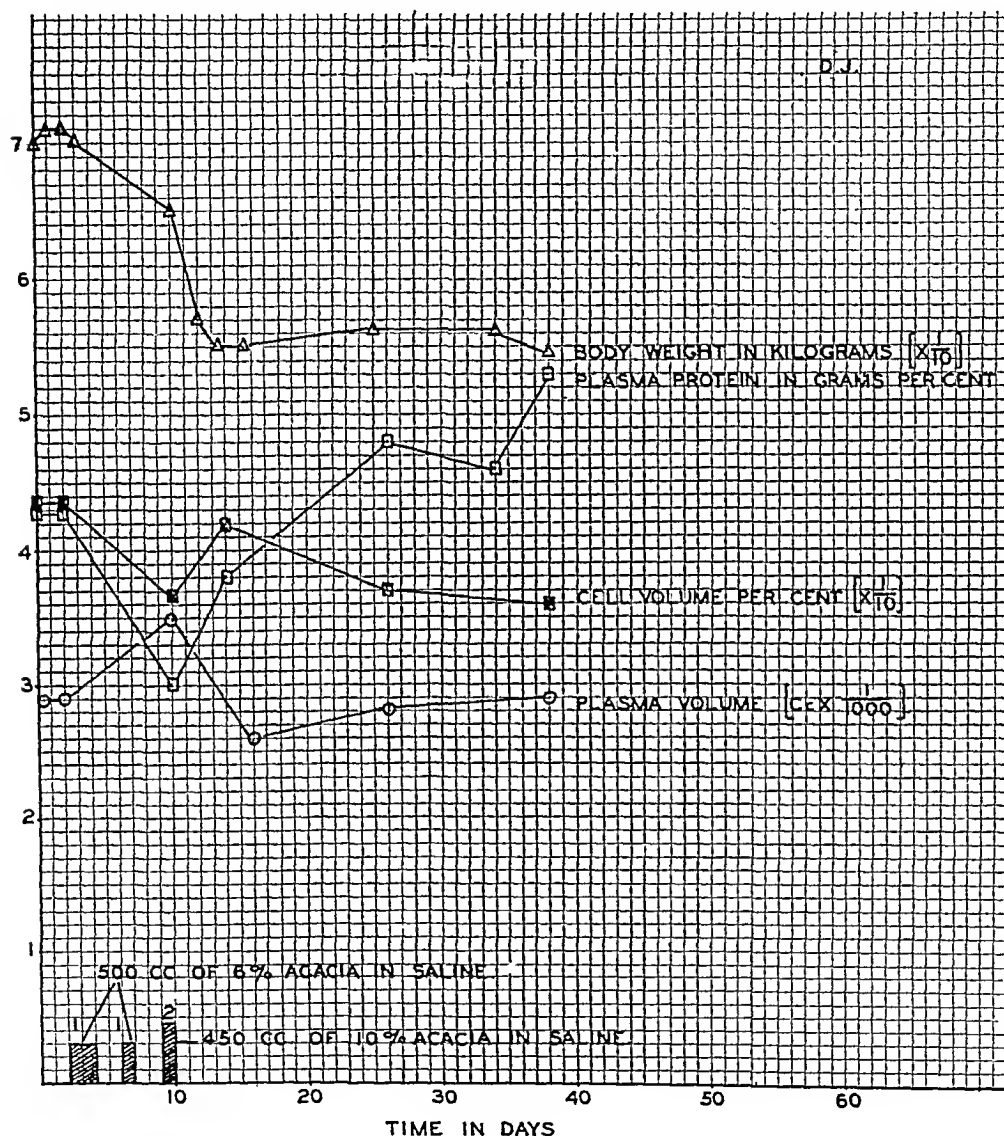


FIG 2

Basal metabolic rate, minus 24 per cent (April 11)

Therapy The patient was placed on a high protein, low salt diet. On April 10, 1935, 500 cc of 6 per cent acacia in normal saline were given intravenously, and the dose was repeated on April 11 and April 14. Diuresis occurred immediately after the first dose of acacia and progressed as shown in figure 2. Another 45 gm of acacia in saline in 10 per cent solution were given on April 17.

Following the acacia injection, as is seen in figure 2, the plasma volume increased considerably, while the cell volume and plasma protein concentration fell, apparently a dilution effect. At the end of the diuresis, the plasma volume diminished in this case and the plasma protein concentration and cell volume rose at the same time. The patient lost a total of 17.2 kilograms of edema fluid during the course of his diuresis. His blood pressure decreased rapidly and remained about 140 systolic and 70 diastolic.

Clinically, there was some evidence that tonsillitis was the factor responsible for the renal lesion. However, in view of the presence of syphilis, cautious anti-syphilitic therapy was initiated including potassium iodide, several doses of bismuth and finally two doses of neoarsphenamine. The patient was improving until on May 12, 1935 he developed tonsillitis. On May 14, 1935 a peri-tonsillar abscess was incised with the liberation of considerable pus. The infection spread rapidly in spite of therapeutic measures and at the same time an acute exacerbation of his nephritis occurred with nitrogen retention. He was discharged against advice on May 12, 1935, his blood non-protein nitrogen having rapidly risen to 90 mg per cent. He died at home the next day.

Case 3 M. W., aged 44, white male

Admitted first on January 8, 1935. Three weeks prior to admission the patient had noted the insidious onset of swelling of the feet and rapid gain in weight. Two weeks before admission, he consulted his doctor who told him he had kidney trouble and placed him on a meat-free, salt-free diet. Edema became progressively worse and he was, therefore, referred to the hospital.

The patient states that he has always enjoyed good health. He has been a rather heavy drinker of corn liquor. There is no history of sore throats, upper respiratory infections or exposure to heavy metals. No history of hematuria.

Physical Examination Blood pressure, 120 mm of Hg systolic and 80 diastolic. A well developed large man weighing 118 kilograms. There is marked pretibial and presacral pitting edema. The heart and lungs are clear. The fundi oculi are normal.

Urine Specific gravity 1.027, albumin 4 plus, no red blood cells. Numerous white blood cells, many small and medium coarse and fine granular casts. No red blood cells on repeated examinations.

Blood Hemoglobin 15.8 gm per 100 cc. Red blood cells 5,030,000 per cu mm. Non-protein nitrogen 31 mg per cent. Total plasma proteins 3.78 gm per 100 cc. Plasma albumin 1.20 gm per 100 cc. Plasma globulin 2.58 gm per 100 cc. Cholesterol 500 mg per 100 cc. Wassermann and Kahn reactions negative.

Kidney function studies Concentration test, maximum concentration 1.027 (corrected for albumin). Urea clearance, 104 per cent of normal (January 9).

Basal metabolic rate plus 3 per cent (January 12).

Therapy He was placed on a high protein low salt diet. On January 11, and again on January 12, 14 and 16, 500 cc of 6 per cent acacia in normal saline were given intravenously. Diuresis occurred following the first injection of acacia and continued as shown in figure 3. At the patient's insistence, he was discharged on January 19, his edema having diminished considerably.

It is seen from figure 3 that following the acacia injection, a large increase in plasma volume occurred with an associated fall in cell volume and plasma protein concentration.

Readmission Readmitted on April 10, 1935 with the complaint of recurrence of edema.

While adhering to the diet following discharge on January 19, 1935, the patient continued to lose edema and his weight reached a low point of 106.7 kilos. However, several weeks after discharge, he resumed his activities and ceased to follow

dietary instructions. Edema returned and he consulted several physicians who, after various therapeutic measures had been tried without success, referred him to the hospital for treatment.

Physical Examination Blood pressure 120 mm of Hg systolic and 70 diastolic. The patient is more edematous now than he has ever been. He weighs 126.25 kilos and later events show that at least 36 kilos of this weight consist of edema fluid.

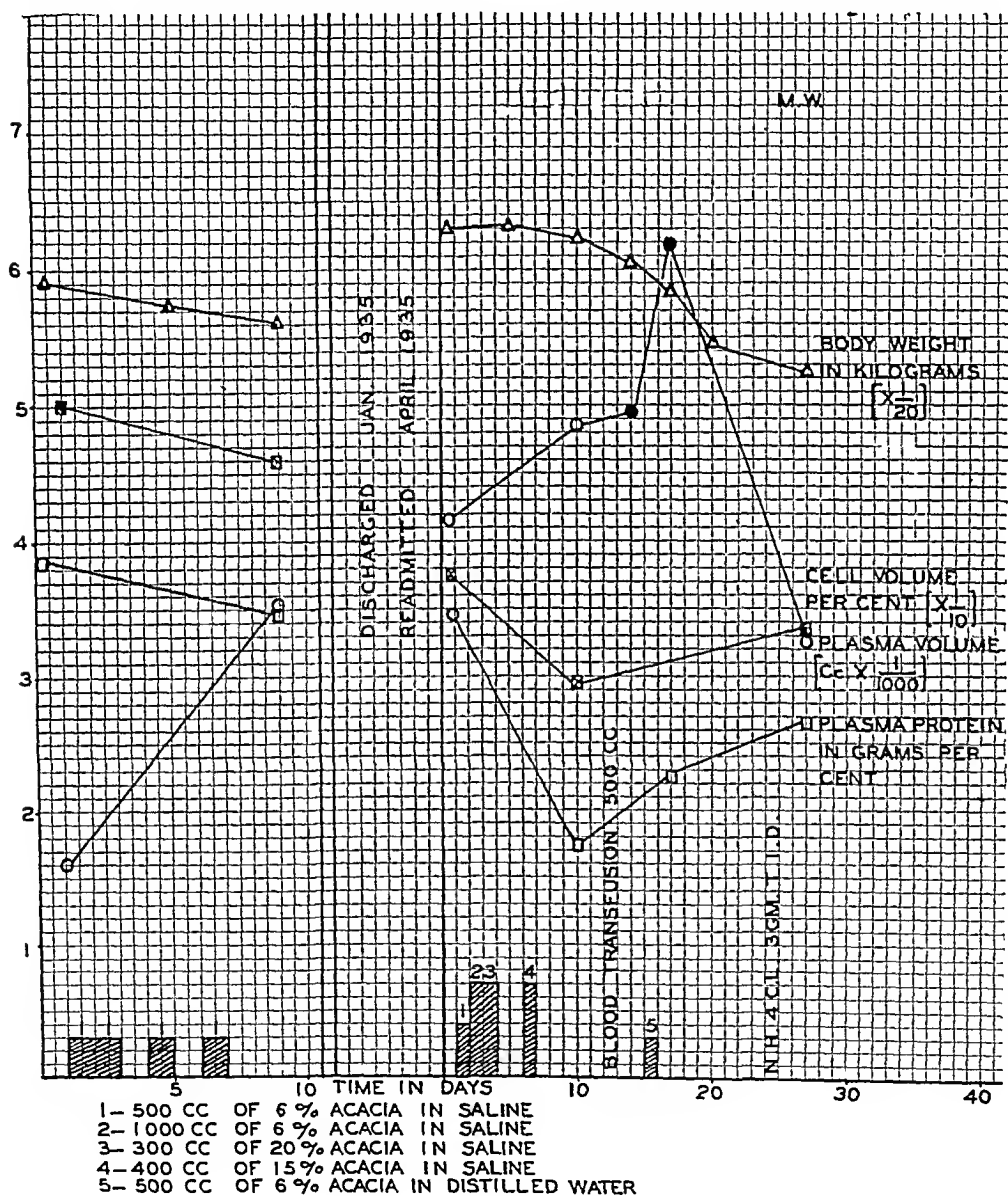


FIG 3

The scrotum is tremendously distended, measuring 102 cm in circumference. Ascites is present. There is no evidence of cardiac failure.

Urine: Specific gravity 1.020, albumin four plus. Microscopic, as before, no red blood cells.

Blood Hemoglobin 14 grams per 100 c c Red blood cells, 4,400,000 per cu mm
 Non-protein nitrogen 35 mg per cent Total plasma protein 3.41 gm per 100 c c
 Plasma albumin 0.71 gm per 100 c c Plasma globulin 2.70 gm per 100 c c

Kidney function studies Urea clearance 97 per cent of normal (May 5)

Basal metabolic rate minus 25 per cent (May 10)

Therapy The patient was placed on a high protein salt free diet Acacia was given at the times and in the quantities and concentrations indicated in figure 3 On April 16, 0.5 c c of salyrgan was given intravenously On April 22, salyrgan 1.0 c c was given intravenously Between April 15 and 20, the patient also received a total of 37 gm of potassium chloride by mouth It is difficult in the face of the employment of several different diuretic agents to evaluate their respective roles in the production of the moderate diuresis which occurred between April 10 and 24 On April 25, 500 c c of 6 per cent salt free acacia in distilled water were given intravenously This injection was followed by a severe chill lasting 30 minutes and a temperature rise to 39.2° C A period of oliguria lasting about 10 to 12 hours ensued However, this was succeeded by a marked and rapid diuresis The plasma volumes charted as of April 25 and April 27 are not actual measurements but are calculated on the basis of observed hemoglobin concentration changes They indicate that following the injection of the last 30 gm of acacia, a large rise in plasma volume occurred Toward the end of the diuresis the plasma volume returned to below the initial figure By this time, the patient had lost 23 kilos, but still had edema Ammonium chloride was started on May 5, 1935 and the patient gradually lost another 12 kilos of edema fluid He was discharged almost edema free on June 6, 1935 His liver was not palpable during either admission

Case 4 Z R, white female, aged 22

The patient was admitted on November 11, 1936 with the complaint of "kidney trouble" In January 1936 the patient noticed the insidious onset of edema of the ankles Several days later she first complained of a severe sore throat Her urine was found to contain large amounts of protein Her family physician advised tonsillectomy which was performed on January 10 The patient remained in bed for one month during which time edema remained marked She resumed her household activities in February 1936 and ate a normal diet She continued to have edema of the legs and face which became more severe despite the employment of a wide variety of therapeutic measures The patient was therefore referred to this hospital for treatment

Physical Examination Blood pressure 110 mm of Hg systolic and 70 diastolic The patient is a well developed young white woman There is marked pitting edema of the subcutaneous tissues from the level of the tenth dorsal vertebra down There is a small amount of pleural fluid in the right chest A moderate amount of ascites is also present The fundi oculi are normal The heart is normal The liver cannot be felt

Urine Amber, specific gravity 1.029, albumin three plus Microscopic Many hyaline casts, rare red blood cells, occasional white blood cell

Blood Hemoglobin 14.6 grams per 100 c c Red blood cells 5,380,000 per cu mm
 Non-protein nitrogen 40 mg per cent Total serum proteins 3.70 gm per 100 c c
 Serum albumin 0.80 gm per 100 c c Serum globulin 2.90 gm per 100 c c Serum cholesterol 621 mg per cent Serum chlorides 554 mg per cent Blood Wassermann and Kahn reactions negative

Kidney function tests Urea clearance 67 per cent of normal (Dec 4, 1936) and 77 per cent of normal (Dec 22, 1936)

Basal metabolic rate minus 12 per cent (Dec 2, 1936)

Therapy The patient was placed in bed and given a diet low in salt and containing 60 gm of protein per day On December 10, 1936 the diet was changed to

120 gm of protein and urea, 60 gm per day by mouth, was given as a diuretic. Since no marked diuresis occurred on this regime, urea was discontinued on December 15, 1936 and acacia injections were started on December 17, 1936. As can be seen in figure 4, diuresis followed the second injection of 500 cc of 6 per cent acacia in normal saline. The patient lost a total of about 10 kilos of edema fluid in seven days and was practically edema free when discharged on December 24, 1936.

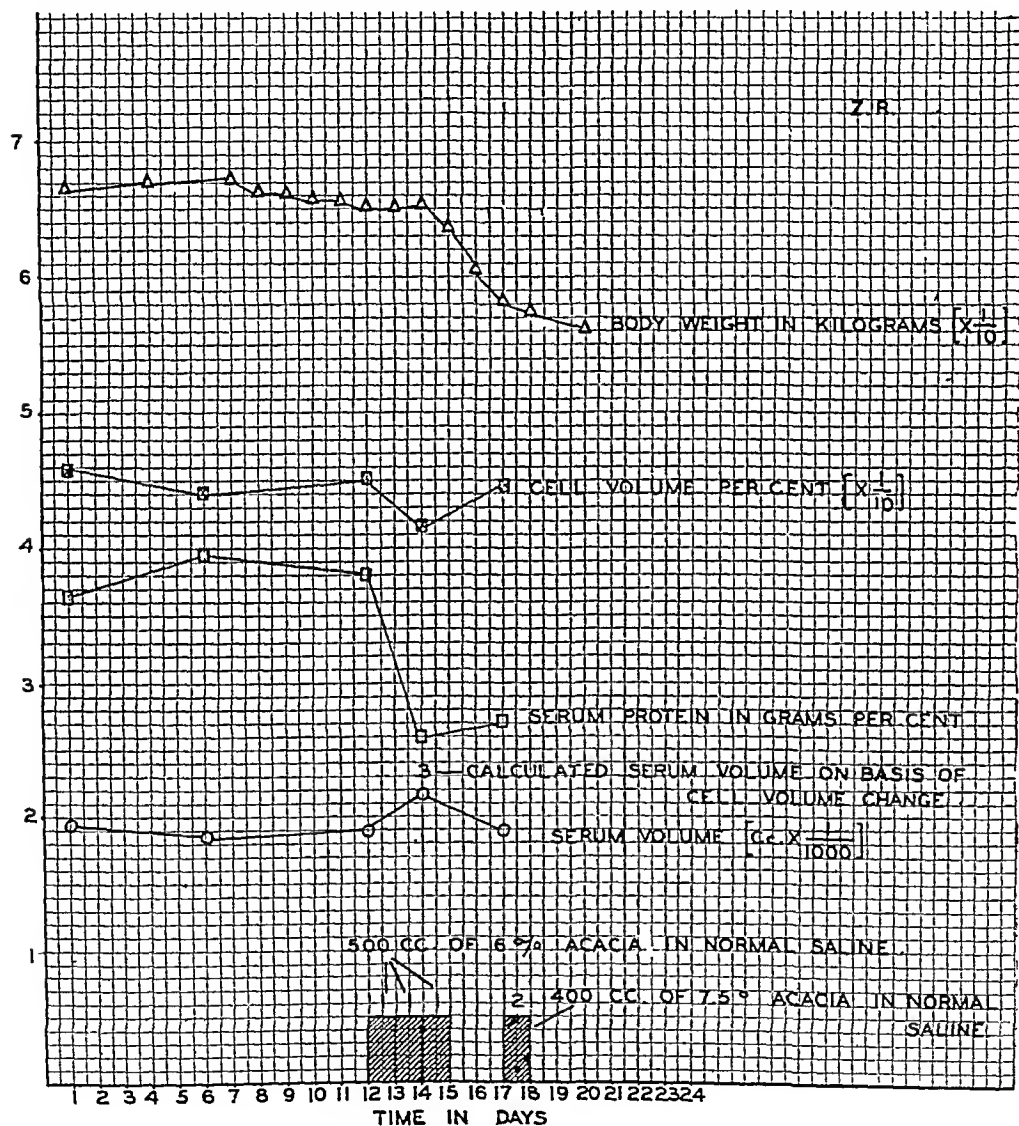


FIG 4

DISCUSSION

Serum Volume Changes and Diuresis When acacia in the concentration of 6 per cent or more is introduced into the blood stream of patients with hypoproteinemia, an immediate increase in plasma colloid osmotic pressure and in plasma volume must of necessity occur. However, the increase in

the plasma colloid osmotic pressure will cause fluid to be attracted to the blood stream and when a state of equilibrium is attained, it may well be that the increase in plasma volume will effectively counterbalance the original increase in plasma colloid osmotic pressure. The final result will, therefore, be an increase in the plasma volume and in the total circulating plasma colloid.

In the present report, the studies of plasma volume have been performed at times significantly distant from the acacia injections, since in this way the more permanent effects of acacia could be investigated. The striking feature of the results is that almost without exception, the persistence of diuresis following the injection of acacia was associated with increase in the plasma volume. In the absence of actual measurements of plasma colloid osmotic pressure, it is impossible to say whether it, too, increased during the periods of diuresis and hypervolemia. However, the decrease in plasma protein concentration noted during the same periods would indicate that if any rise in plasma colloid osmotic pressure did occur, it was probably of small magnitude. Since the most consistent change following acacia injection was the increase in plasma volume, it seems logical to suspect that this change was the one responsible for diuresis. This suggestion was originally advanced by Peters⁸ in a stimulating discussion of the mechanism of acacia diuresis in nephrosis which concluded with the statement that "It may well be the fullness of the blood stream which provokes the diuretic response on the part of the kidneys."

The manner in which the "fullness of the blood stream" provokes diuresis is not apparent from the data at hand. It is, however, probable that the diuresis associated with increases in plasma volume is due to increased filtration of urine. This may be due to the opening of more glomeruli by the larger volume of blood or to an increase in the rate of blood flow through the kidneys. In the absence of actual measurements of these variables, the mechanism provoking diuresis must remain obscure.

If increase in plasma volume provokes diuresis in nephrotic states, some of the so-called "spontaneous" diureses which we occasionally see may thus be explained. When these diureses have occurred in the absence of any change in the plasma protein concentration, they have usually been classed as exceptions to the Starling theory. However, we now have evidence that large fluctuations in plasma volume and hence in the total circulating colloid may occur in nephrotic states without any changes in the plasma protein concentration.⁹ During the "spontaneous" diureses, despite constant plasma protein concentrations, large rises in the total circulating colloid may have occurred. Such rises would act much like acacia in initiating and maintaining diuresis. Our data do not support the view that the absolute volume of the plasma at any given time is the factor responsible for diuresis. However, they do support the thesis that acutely induced increases in the plasma volume provoke diuresis. The cause for this is probably to be found in the fact that gradual changes in plasma volume are compensated for,

while the more acute changes exceed, for a time at least, the ability of the body to compensate

Serum Protein Changes Following the injection of acacia, in accord with the report of Dick and associates,³ the plasma protein concentration decreased. This change was due in part to hemo-dilution. However, in three instances, hemo-dilution alone did not account for the decrease in plasma protein concentration. Measurements of the plasma volume in these patients revealed that the *total circulating plasma protein* (derived by multiplying the plasma volume by the plasma protein concentration), had actually decreased following the injection of acacia. It is not to be inferred that the regeneration of plasma protein was impaired, for in one carefully studied case,¹⁰ regeneration of plasma protein remained active following the use of acacia. However, with diuresis, the urinary loss of protein increased sufficiently to account for the observed reduction in the total circulating plasma protein. The explanation for this increase in proteinuria is not evident but is now being sought in this clinic. At present, it is our belief that the increased proteinuria following acacia injection is due to increased glomerular filtration and not to a toxic action of acacia on the glomeruli. In accord with this belief are the data of Bing¹¹ who has suggested that changes in the degree of proteinuria in the same patient reflect changes in glomerular filtration.

Red Cell Volume Changes The decrease in red cell volume following acacia therapy is largely a dilution effect.

Practical Considerations It is apparent that in the cases here reported, diuresis was provoked by acacia in much smaller quantities than those used by others.²⁻³ Our studies indicate that the aim of acacia therapy is to increase the plasma volume, and this may be attained with relatively small dosage of acacia. We are now using intravenous injections of 500 c.c. of 6 per cent acacia in normal saline as a dose for average adults, and this is repeated at daily intervals for three or four days. If acacia is going to be effective, results should be apparent with this dosage in most cases. We see no point in forcing dosage much past this limit if no diuresis has resulted. If diuresis does occur, 30 gram doses may be repeated at intervals which will of necessity vary with individual cases. The plasma albumin level should be watched closely and if it falls too sharply, acacia therapy should be discontinued until the albumin level has been substantially improved.

In selecting cases for acacia therapy, the following suggestions may be of value. A previous adequate trial on a high protein salt-poor diet and diuretics such as urea or members of the saline diuretic group is definitely indicated in all cases. These therapeutic measures may well be supplemented with others aimed at increasing the plasma volume and plasma proteins, e.g., transfusions of whole blood, serum or plasma. If these measures fail, acacia therapy should be considered. Should an untoward reaction occur, the safest procedure is to stop using acacia. The use of acacia need not be

limited to cases of so-called nephrosis, for our results have been equally good in cases of chronic active glomerulonephritis in the nephrotic stage

CONCLUSIONS

1 Acacia provokes diuresis in nephrotic edema by increasing the plasma volume

2 A method of administration of acacia is presented, based upon the above concept of its mode of action, and involving the use of relatively small doses

3 The so-called deleterious effects of acacia described by other writers have been explained on grounds other than those of toxicity of acacia

4 Acacia has a definite place in the therapy of properly selected cases of nephrotic edema

I am deeply indebted to Dr John P Peters for his valuable advice

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RECENT STUDIES ON THE EXCRETION OF MALE SEX HORMONES IN MAN ⁴

By F C KOCH, *Chicago, Illinois*

ALTHOUGH androsterone and dehydroandrosterone, two substances of androgenic character, have been separated from human urine, very little is known as to the significance of their occurrence and still less as to the fluctuations in the rate of excretion in health and disease. It is generally assumed that these substances are waste products formed from testosterone secreted into the blood stream by the gonads, but it is just as reasonable to expect that one or both of these urinary products may be precursors of testosterone or that they, or still other androgenic substances, may originate in part in other tissues or be present in our food.

A survey of the literature ¹ reveals that too many investigators have attempted to answer some of these questions by extraction and biological assay methods which are practically worthless for quantitative purposes. In this paper I propose to present a summary of some of the results which my colleagues and I have published on this problem in more detail elsewhere ^{1, 2, 3}.

By means of the comb-growth response in the capon ⁴ and a complete extraction procedure for urine, ⁵ we arrive at values which are distinctly higher than the highest reported elsewhere and 20 to 60 times the lowest reported by others ^{6, 7}. Our higher values are due to two factors—the complete extraction of the urine, the liberation of androgenic activity by acid hydrolysis from what appears to be a conjugated form, and the prevention of the subsequent destruction thereof by acid by limiting the hydrolysis to the time of maximum yield ³. Table 1 clearly shows that 15 minutes' acid-hydrolysis leads to a 70 to 160 per cent increase in androgenic units, but that two hours' boiling again leads to a loss of activity. The nature of the con-

TABLE I

The Effect of Length of Time of Acid Hydrolysis in Three Urines on the Yield of Androgens

Sample	International androgenic units per liter obtained when boiled for					
	0 min	¼ hr	1 hr	2 hrs	6 hrs	12 hrs
A	20	53	37	29	20	—
B	31	50	—	35	—	25
C	27	66	54	38	33	—

* Presented at the St. Louis meeting of the American College of Physicians, April 19, 1937.

From the Department of Biochemistry, The University of Chicago

jugated form, of the destructive process, and the significance of the conjugation, remain to be determined

Our studies on normal men and women covered urine collections for 27 to 45 consecutive days. The collections from men usually were pooled for three consecutive days. From the women we received two-day samples except during menstruation, when the excretions were pooled for the period. These urines were completely extracted, the androgenic and estrogenic activities separated from each other and assayed on capons and spayed rats respectively.

The results are given in tables 2, 3, and 4. In seven of the eight subjects we hydrolyzed the urine for two hours because at the time we had not discovered the importance of a brief period of hydrolysis. In subject 4, we limited the hydrolysis to 15 minutes, hence the greater yield of androgenic units in this individual. In both men and women we observe marked daily fluctuations in the urinary excretion of androgens and estrogens. The rates of excretion of the two activities bear no relation to each other.

Only one of the normal men gave an indication of a cycle in the rate of excretion of androgenic substances. Although the daily variations for a given individual and for the group of men are marked, the daily averages for the four individuals are remarkably constant, ranging from 63 to 68 international androgenic units. The averages for the estrogenic activity are also remarkably close, that is, 9 to 12 gamma theelin per day. By dividing the androgenic units per day by the gamma of theelin per day, we obtain

TABLE II

The Daily Urinary Excretion of Androgenic and Estrogenic Activities by Four Normal Men
 "An" designates international androgenic units per day
 "Es" designates estrogenic activity as gamma of theelin per day

Subject 1 age 27 yrs				Subject 2 age 26 yrs				Subject 3 age 30 yrs				Subject 4 age 35 yrs			
Days	An	Es	An/Es	Days	An	Es	An/Es	Days	An	Es	An/Es	Days	An	Es	An/Es
3	25	10	3	3	40	5	8	3	30	12	3	2	25	8	3
"	39	8	5	"	28	10	3	"	37	10	4	3	69	16	4
"	50	4	12	"	27	2	14	"	45	10	5	"	25	5	5
"	34	10	3	"	37	18	2	"	52	26	2	"	38	13	3
"	38	8	5	"	32	2	16	"	42	10	4	"	23	16	2
"	24	8	3	"	65	3	22	"	24	4	6	"	58	11	5
"	33	5	7	"	20	2	10	"	79	14	6	"	65	11	6
"	37	5	8	"	41	20	2	"	49	10	5	"	42	10	4
"	45	10	5	"	53	3	18	4	41	11	4	"	41	16	3
"	48	5	10	"	36	2	18	"	36	2	18	"	31	10	3
"	63	18	4	"	52	18	3	3	44	2	22	4	30	21	2
"	38	10	4	"	lost			"	40	29	1	3	34	10	3
"	34	10	3	"	46	18	3	"	lost						
"	29	9	3	"	62	8	8	"	13	14	1				
Ave values	38	9	4.2		41	9	4.6		41	10	4.1		40	12	3.3

The urine of these subjects was boiled two hours before extraction

TABLE III

The Daily Urinary Excretion of Androgenic and Estrogenic Activities by Four Normal Women
 "An" designates international androgenic units per day
 "Es" designates estrogenic activity as gamma of theelin per day

Subject 1 age 34 yrs				Subject 2 age 31 yrs				Subject 3 age 24 yrs				Subject 4* age 23 yrs			
Days	An	Es	An/Es	Days	An	Es	An/Es	Days	An	Es	An/Es	Days	An	Es	An/Es
5 M	22	7	3	3	20	44	0.5	2 M	22	5	4	2	70	21	3
2	42	31	1	2	35	38	0.9	2 M	13	5	3	5 M	45	4	11
"	21	25	0.8	"	30	22	1	"	28	10	0.4	2	45	8	6
"	31	28	1	"	18	53	0.3	"	36	21	2	"	45	8	6
"	29	18	2	"	27	30	0.9	"	19	9	2	"	42	11	4
"	23	21	1	"	27	30	0.9	"	22	25	0.9	"	49	28	2
"	19	40	0.5	"	26	60	0.4	"	42	21	2	"	lost		
"	20	35	0.6	"	28	40	0.7	"	16	16	1	"	50	25	2
"	22	30	0.7	"	25	40	0.6	"	46	22	2	"	53	16	3
"	17	34	0.5	"	26	40	0.7	"	lost			"	60	16	4
"	lost			"	18	18	1	"	23	27	0.9	"	63	41	2
"	25	30	0.8	7 M	26	13	2	"	36	18	2	"	56	32	2
								"	29	28	1	"	85	28	3
								"	20	10	2	"	68	24	3
								"	24	22	1				
Ave values	25	27	0.93		26	36	0.72		28	18	1.6		56	20	2.8*

* The urine of subject 4 was hydrolyzed for 15 minutes, the others for 2 hours

M = menses

TABLE IV

A Summary of the Average Values from Tables II and III

"An¹⁵" designates the international androgenic units per day by the 15-minute boiling-procedure

"An²" the same by the 2-hour boiling-procedure

"Es" designates the estrogenic activity as gamma of theelin per day

Men						Women					
Subject	An ¹⁵	An ²	Es	An ¹⁵ /Es	An ² /Es	Subject	An ¹⁵	An ²	Es	An ¹⁵ /Es	An ² /Es
1	63*	38	9	7.0	4.2	1	42*	25	27	1.6	0.93
2	68*	41	9	7.6	4.6	2	43*	26	36	1.2	0.72
3	68*	41	10	6.8	4.1	3	47*	28	18	2.5	1.5
4	66*	40	12	5.5	3.3	4	56	34*	20	2.8	1.7
Average				6.9	4.1					2.0	1.2

* These values are calculated on the assumption that the yield of androgenic activity is increased by 66 per cent over the 2-hour hydrolysis if boiled 15 minutes instead

what we call our An/Es ratios. This ratio ranges from 1 to 22 for the men, but when averaged again covers a relatively narrow range of 5.5 to 7.6

In the normal women the rate of excretion of androgens is also variable and of a high order, but distinctly lower than in men. The averages are again relatively constant as shown in table 4. The daily excretion of estrogens also varies considerably in normal women, but tends to be higher than in men. There is good evidence of the periodic rise and fall in the excre-

tion of estrogens in relation to the menses. The excretion of the estrogens generally is higher 7 to 14 days after the onset of menstruation and again 6 to 12 days before the next period. The excretion is lowest during menstruation. The An/Es ratios also vary tremendously in each of the four women, ranging from 0.3 to 11, but the averages range from 1.2 to 2.8 for women as compared with 5.5 to 7.6 for men (table 4). This change in ratio is due to the fall in excretion of androgens and rise in estrogens in women as compared with men.

In the present state of our knowledge we do not know how to explain these remarkable fluctuations. It is very probable that the exogenous source of these hormones is negligible because their presence in foods is limited to exceedingly small amounts and because their absorption probably is relatively difficult. Whether the endogenous source is limited to the gonads or whether the suprarenals and liver are also involved in the healthy individual, remains to be determined.

Studies in Hypogonadism. In two castrates we found 1 to 3.5 international capon units of androgens and 3 to 4.5 gamma theelin per liter of urine. These amounts may easily be of exogenous origin. In seven eunuchoids, the daily excretion varied from 5 to 19 international capon units of androgens and 1 to 9 gamma theelin per day. In two cryptorchids, the values were 9 to 31 and 1 to 6, respectively. Apparently there is no doubt that these extreme conditions lead to a very low excretion of both sex hormones. However, in spite of the low absolute excretion, the An/Es ratios ranged from 0.3 to 31.

Studies in Gynecomastia. In three cases of gynecomastia we found 0 to 37 androgenic units and 5 to 15 gamma theelin excreted per day. The An/Es ratios ranged from 0.1 to 2.5, but no excess excretion of estrogens was observed.

Studies in Virilism. In thirteen cases of virilism without obvious adrenal involvement, the daily excretion of androgens ranged from 5 to 55, of estrogens, from 4 to 19, resulting in ratios ranging from 0.2 to 7.5. In four cases with adrenal involvement, the androgen excretion values were 0, 44, 69, and 480 international units per day, and 4 to 8 gamma estrogens per day. The case with the highest value gave the An/Es ratio of 60. In general there appears to be a tendency to an increased An/Es ratio with a fall in excretion of estrogens in cases of virilism. This is, however, not always true. The patient with an excretion of 480 international androgenic units is of special interest for several reasons. First, because after removal of the adrenal cancer, the hirsutism disappeared, second, because absorption spectra studies indicate a possibly closer chemical relation of the androgenic substance to testosterone than to androsterone or dehydroandrosterone, and third, because studies by others on an oxidation product of a cortical adrenal hormone demonstrate its relation to testosterone chemically as well as biologically^{8,9}. This oxidation product was found to be one-sixth to one-

fourth as active as androstosterone in the capon. Others^{10, 11} have found exceedingly high concentrations of androgens in the urine from cases of adrenal tumors.

SUMMARY

1 There are marked daily fluctuations in the urinary excretion of androgens and estrogens in normal men and women.

2 The average daily excretion of androgens is 63 to 68 international units in men and 42 to 56 units in women.

3 The average daily excretion of estrogens, calculated as gamma of theelin, is 9 to 12 gamma for men and 18 to 36 gamma for women.

4 In male castrates, exceedingly small amounts of sex hormones are found in the urine.

5 In eunuchoids the excretions of sex hormones are distinctly lower than in normal individuals.

6 In gynecomastia, no excess excretion of estrogens was observed.

7 In virilism there is a tendency toward a lower excretion of estrogens with a normal or higher excretion of androgens.

8 In some cases of virilism with adrenal involvement, the excretion of androgens is exceedingly high.

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MYXEDEMA, PRESENTATION OF A GROUP OF CASES ILLUSTRATING PHASES OF THE DISEASE WHICH ARE RECEIVING ATTENTION IN RECENT LITERATURE

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RECENT investigations of myxedema have greatly increased our knowledge of the disease. Attention has been directed to newly recognized symptoms, to changes in the cholesterol and carbohydrate metabolism, and especially to the heart findings. The following case histories are presented because they illustrate these and other features of the disease. Since the cardiovascular changes in myxedema have been the object of so much discussion, they have been stressed in this article. A hypothesis to explain these changes on a pathological physiological basis is presented.

CASE REPORTS

Case 1 *Spontaneous myxedema in a woman aged 51, typical signs and symptoms, chronic valvular disease of heart in association with "myxedema heart", markedly dilated heart decreasing in size with thyroid therapy, increase in voltage in electrocardiogram with treatment, small maintenance dose of thyroid*

B. G., a white woman of 51, entered the clinic in January 1934 complaining of "shortness of breath," "lack of life," and "difficulty in hearing." One sister had diabetes and her father had had a cancer of the eyelid. Menopause occurred eight years ago. Her knees were stiff and swollen at 19 years of age. Patient believed that she was quite well until six or seven years ago. At that time she noticed that her eyelids became puffy, shortly afterwards her feet became edematous and recently her entire body, especially her abdomen, had begun to swell. She lacked energy. Memory was poor and she could neither think nor act rapidly. Her hearing had become poor and her voice husky in recent years. She could not stand cold weather. Her hands did not perspire. The skin had become dry and scaly. In spite of a poor appetite, weight had not been lost.

Examination revealed a small white woman who walked with a slow shuffling gait. She reacted slowly and talked slowly in a rather coarse, low-pitched voice. The skin was pale, dry, coarse and scaly. On each cheek was a small area of cyanosis. Hair was present only on the eyebrows, scalp, and pubis and in these regions it was scant, coarse, and brittle. The facial expression was dull and heavy. The cheeks were puffy and the lips thick. The thyroid could not be palpated. A few fine rales were heard at the bases of both lungs posteriorly. The blood pressure was 138 systolic and 102 diastolic. The pulse rate was 60 per minute with a regular rhythm. The heart was enlarged to percussion. A systolic murmur, most intense at the apex, was heard over the entire precordium. There was very little evidence of peripheral arteriosclerosis. The abdomen was distended but no shifting dullness was obtained. The liver was not palpated and was not down to percussion. A pitting edema of both legs was present.

The basal metabolic rate was minus 31, the blood cholesterol 300 mg per 100 c c ,

* Received for publication February 20, 1937

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the urine normal and the blood Wassermann test negative. The blood contained 3,470,000 red blood cells per cu mm and 9.8 grams of hemoglobin per 100 c c. The gastric analysis (test meal) showed no free hydrochloric acid and a total acidity of 8 degrees. The sugar tolerance curve (175 grams of glucose per kilogram body weight was given in all sugar tolerance tests) showed a somewhat diminished tolerance, the peak was at 192 in the first hour with a return to normal at three hours. All complexes in all leads of the electrocardiogram were of low voltage. Left axis deviation was present. The chest roentgen-ray (figure 1, A) revealed a bilaterally enlarged heart.

One-half grain of desiccated thyroid (Lilly's) was found to be sufficient to keep the basal metabolic rate within normal limits. Marked clinical improvement was evident shortly after starting treatment. The patient began to react more rapidly, walk more rapidly, and speak more rapidly. The puffiness gradually left her cheeks and eyes and the dull, myxedematous facies gave way to a more alert expression. The skin became more smooth and oily and hair began to grow more abundantly. Fatigue and weakness diminished. The edema of the extremities left. As the heart action became more vigorous, the systolic murmur remained and increased somewhat in intensity. This finding, combined with a history of "rheumatism" at the age of 19, made the diagnosis of rheumatic heart disease with mitral insufficiency very probable.

The remarkable changes which occurred in the size of the heart are illustrated in figure 1. On 4/12/34, the date of the last film, the basal metabolic rate was plus eight, the pulse rate 62 per minute, the blood pressure 135 systolic and 90 diastolic, the hemoglobin 12.8 grams per 100 c c and the red blood cell count 5,100,000 per cu mm. The electrocardiogram showed an increase in voltage of all complexes in all leads, the left axis deviation persisted. A gastric analysis still showed an achlorhydria with a total acidity of 10 degrees. A sugar tolerance on 5/27/34 revealed a peak of 220 in one hour with a return to normal in three hours.

Note (1) The very small dose of desiccated thyroid required to keep the basal metabolic rate at normal and produce the changes noted. (2) The remarkable decrease in heart size under thyroid therapy. (3) The low voltage in the electrocardiogram associated with the enlarged heart and the increase in voltage as the heart diminished in size under thyroid therapy. (4) The association of "myxedema heart" with a valvular lesion probably of rheumatic origin. (5) The family history of diabetes in a sister and the presence of a somewhat decreased sugar tolerance in the myxedematous state with a further decrease in tolerance after treatment.

Case 2 Spontaneous myxedema in a woman aged 31, typical signs and symptoms, including menorrhagia, variations in heart size with degree of hypothyroidism, association of rheumatic heart lesions and "myxedema heart"

M. S., a white woman, aged 31, entered the clinic on 3/24/31 complaining of extreme dyspnea on exertion and menorrhagia. About two years previous to her entrance she began to notice difficulty in breathing on exertion. She suffered constantly from extreme lassitude. In the last few years although her appetite had remained the same, she had gained 30 pounds in weight. She complained also of frequent headaches, occasional numbness of the right forearm and hand, painful and excessive menses, and sterility. The family history was essentially negative. Her husband had tuberculosis. There was no history of rheumatic fever, chorea, or frequent sore throats. Physical examination on admission showed an obese woman with puffy face and swollen eyelids, dry and scaly skin, and coarse hair. Blood

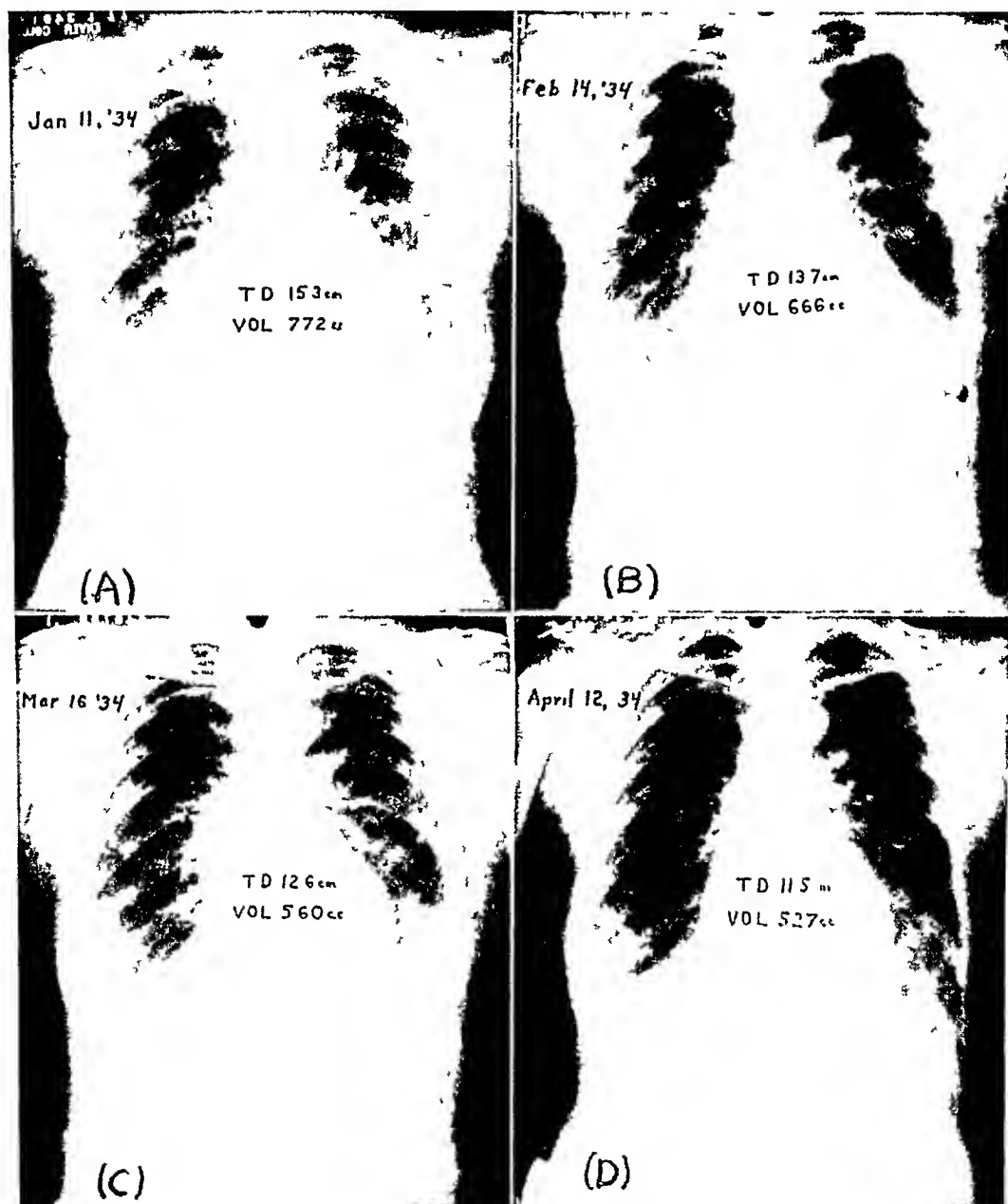


FIG 1 Case 1 (A) Before treatment BMR —31 Blood cholesterol 300 mg per 100 cc
 (B) One month after starting treatment BMR plus 3 Blood cholesterol 180 mg per 100 cc
 (C) Two months after starting treatment BMR plus 1
 (D) Three months after starting treatment BMR plus 8

pressure was 120 systolic and 80 diastolic Pulse rate 62 No murmurs were heard The basal metabolic rate was minus 30

Under thyroid therapy the patient improved marvelously In August 1932, however, she stopped coming to the clinic She continued to take thyroid for a number of months and then stopped In August 1934 she returned with very much the same story as on her first admission She felt weak, tired easily and had no

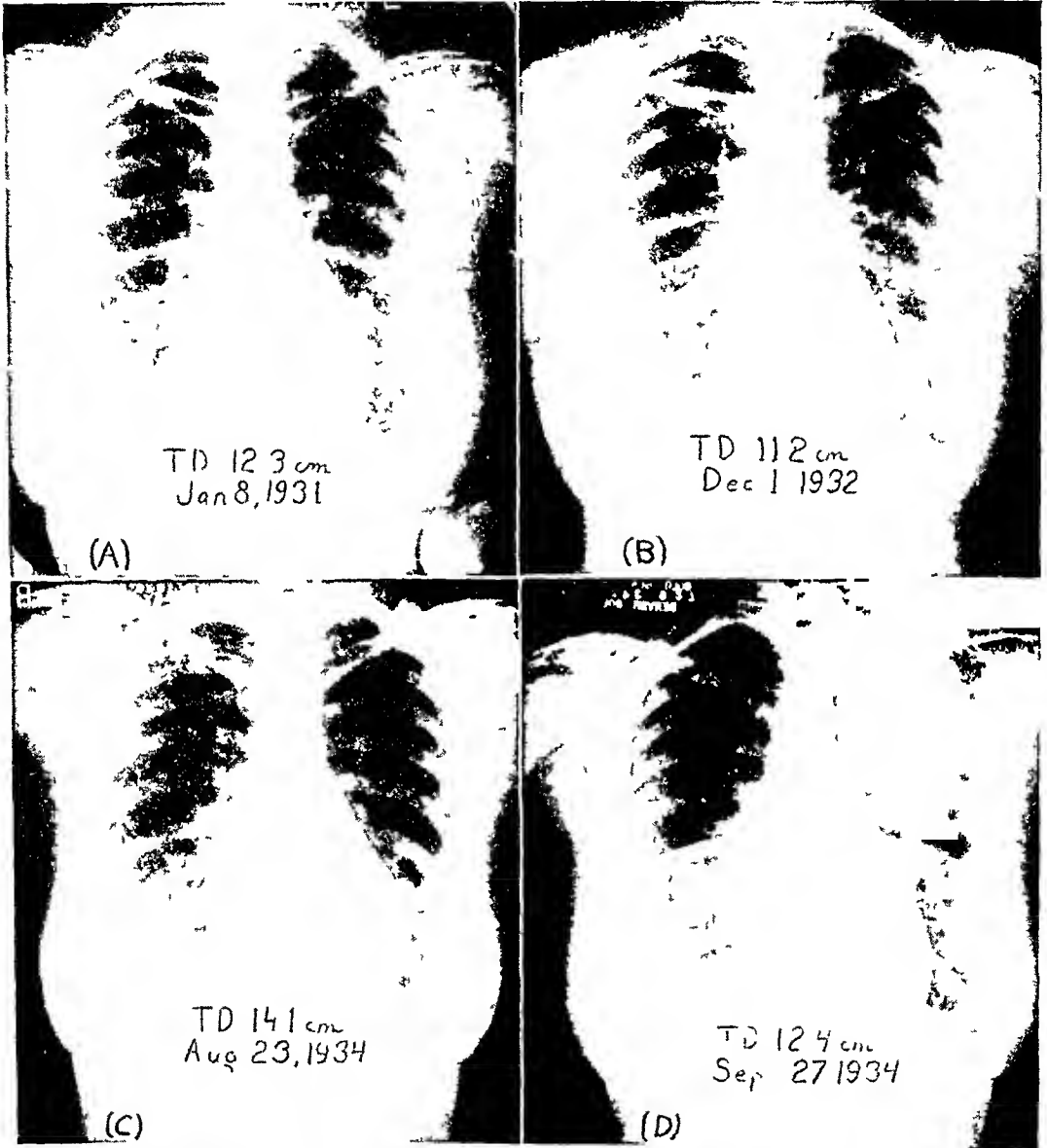


FIG 2 Case 2 (A) Two months before patient's first entrance into clinic BMR at time of admission into clinic was —30

(B) Patient had been taking thyroid for over one and a half years BMR —10 It must be noted in comparing the plates that although in the other three plates the diaphragm is almost at identical levels, in this plate it is slightly lower

(C) Patient had been without thyroid for about one and a half years BMR —36

(D) After about four weeks of thyroid therapy BMR —14

energy. Her entire body seemed, to her, to be more or less swollen. Her skin had recently become coarse and her finger nails brittle. Examination revealed most of the signs of myxedema: slow response, dry, coarse skin, puffy cheeks and swollen eyelids. The heart was enlarged to percussion. No murmurs were heard. The basal metabolic rate was minus 34 and blood cholesterol 236 mg per 100 c.c. The sugar tolerance curve was normal. Electrocardiogram revealed a low voltage of all complexes.

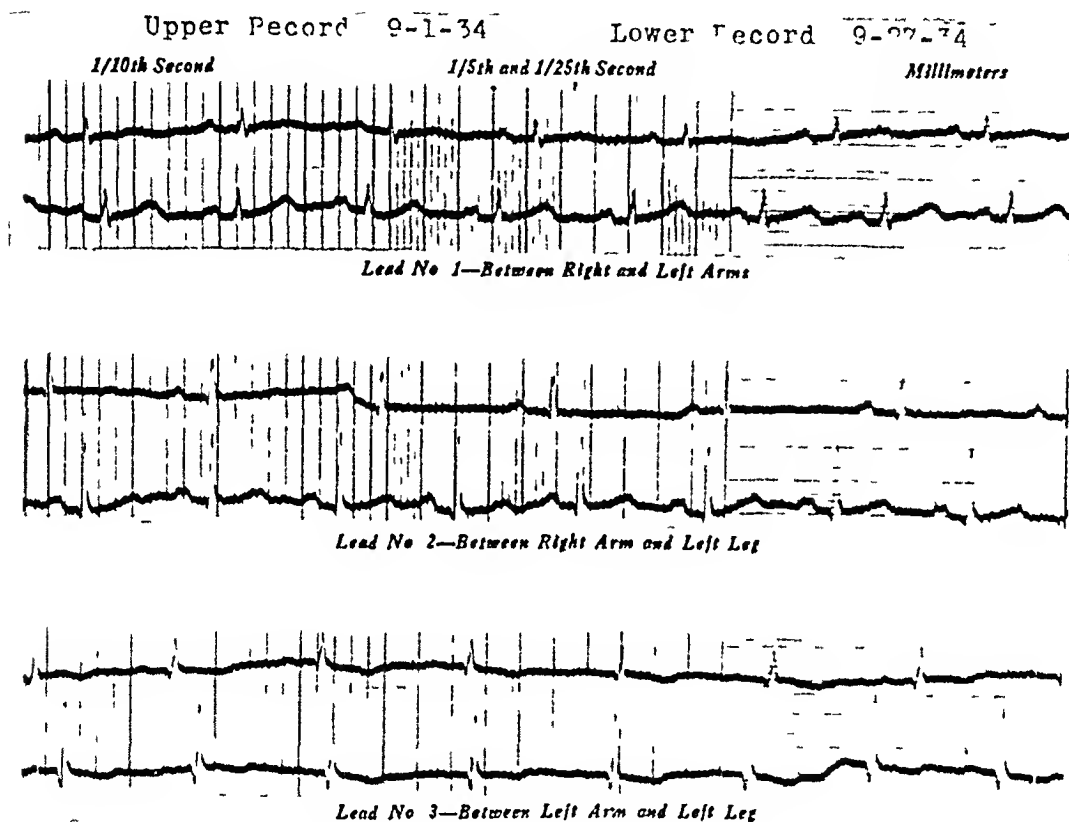


FIG 3 Electrocardiographs taken on Case 2. Upper tracing on 9-1-34 before thyroid therapy. Lower tracing on 9-27-34 after about four weeks of treatment.

Four weeks after starting thyroid therapy (final maintenance dose was three grains of desiccated thyroid daily) the patient showed the usual signs of improvement. Examination of the heart at this time showed it to be normal in size. Very definite mid-diastolic, presystolic, and systolic murmurs were heard and the diagnosis of mitral stenosis and insufficiency was beyond question. These murmurs were not heard before treatment in spite of several careful examinations. The interesting changes which occurred in the size of the heart are illustrated in figure 2. The electrocardiogram showed increased voltage throughout (figure 3). A sugar tolerance taken eight months after starting treatment was normal. A blood cholesterol at the same time was 137 mg per 100 c.c.

Note (1) Variations in heart size corresponding to degree of hypothyroidism. (2) Association of "myxedema heart" and rheumatic heart lesions. (3) Menorrhagia, which is referred to as of frequent occurrence.

in myxedema (4) Absence of the characteristic murmurs of mitral stenosis and insufficiency in the hypothyroid state Several factors are probably involved Most important is probably the decrease in velocity of blood flow The diastolic murmurs of mitral stenosis will sometimes disappear when auricular fibrillation sets in, and the explanation usually given is that the absence of murmurs results from the decrease in velocity of blood flow The conditions appear analogous The increased viscosity of the blood in myxedema may hinder the production of murmurs The possibility of dilated rings in a dilated heart must be considered

Case 3 Spontaneous myxedema in a 16 year old girl, typical signs and symptoms, heart size within normal limits before treatment with decrease in size after treatment, abnormal electrocardiographic features with change to normal after thyroid therapy

S. C., a white girl, aged 16, entered the clinic on 1/15/34 with a history of being tired and cold all the time, having no appetite, swelling of the feet, and infrequent menses Symptoms had been present for the last five years and during that time she had been told by a private physician that she had heart and kidney trouble and had been in a hospital with a diagnosis of cardio-renal disease Physical examination revealed enough of the signs of myxedema to make the diagnosis quite evident—mental retardation, pale, dry skin, dull facies, marked supraclavicular pads of fat (figure 4) and slow pulse The heart was apparently normal in size with a transverse diameter of 10.3 cm There was no edema of the extremities The basal metabolic rate was minus 41, blood cholesterol 350 mg per 100 cc, fasting blood sugar was 64 mg per 100 cc The electrocardiogram revealed flat T-waves in all leads, right axis deviation, and a QRS spread of 0.12 second The patient showed the usual

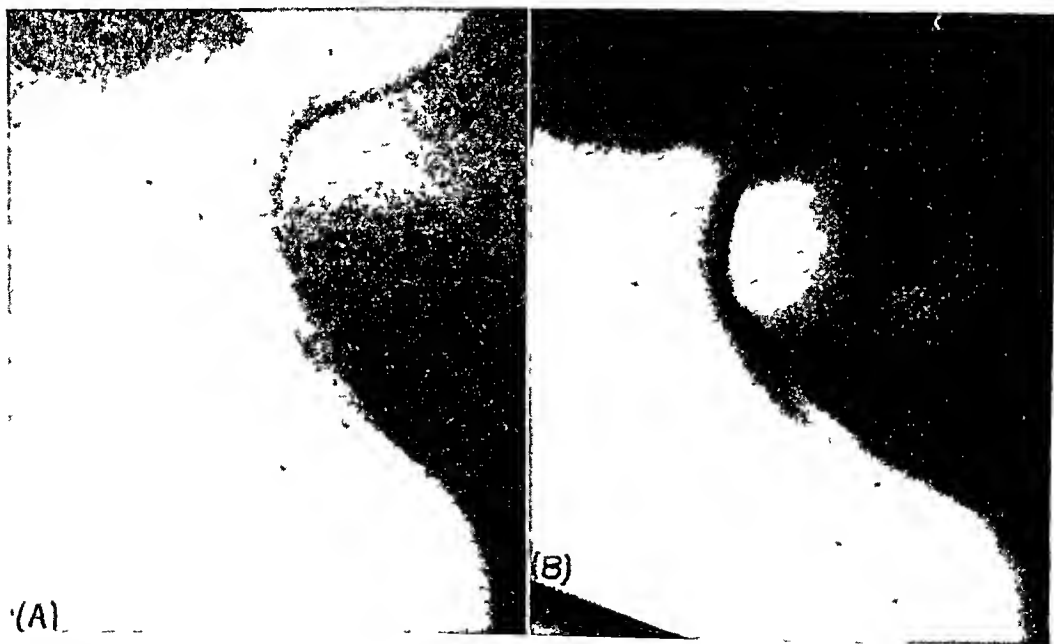


FIG 4 Case 3 (A) Taken on 1-12-34 before starting thyroid therapy (B) Taken on 5-28-34 after about five months of treatment Note loss of the supraclavicular pad of fat

marked and gratifying improvement with thyroid. The transverse diameter of the heart decreased to 9.6 cm. The electrocardiogram now showed T-waves of good voltage in all leads, normal axis deviation, and a QRS spread of 0.08 second.

Note (1) Change in heart size even though the heart was apparently normal in size before treatment. (2) Marked electrocardiographic changes with a heart of apparently normal size. (3) The erroneous diagnosis of renal, or cardio-renal disease, not infrequently made in these cases.

Case 4 Postoperative myxedema in a woman aged 27, mental reactivity out of proportion to myxedematous state, abnormal electrocardiograph with heart of normal size, marked anemia responding only to non administration, prolonged tendon reflexes

J. B., a white woman, aged 27, entered the clinic on 11/27/34 complaining of "nervousness and palpitation" of several years' duration. In 1928 she noticed some enlargement of her neck, her nervousness and palpitation began about the same time. The next year exophthalmus, more prominent on the left, appeared. In July 1933 the diagnosis of toxic goiter was made and a thyroidectomy performed. This resulted in a temporary improvement of the symptoms but the nervousness and palpitation soon returned. On entrance into the clinic she complained also of being very weak and tiring easily. Although her appetite was poor, it was significant that she had not been losing weight. For several months a puffiness of the face and eyes had been noticed. She was sensitive to cold and her skin had become dry and coarse. Menstruation had begun at 14 and had been regular and normal until the toxic goiter developed, when the flow became excessive, after thyroidectomy, the flow became normal.

Patient was very talkative and spoke rather rapidly. She thought and responded with normal or increased rapidity. In general, her behavior corresponded more with that of a hyperthyroid than a hypothyroid individual. The facies presented a peculiar combination of the residue of hyperthyroidism (exophthalmus) and the features of hypothyroidism (puffy cheeks and eyelids, pasty skin). The skin was pale, dry and scaly. The blood pressure was 100 systolic and 76 diastolic. Pulse rate was 70 per minute and regular. Heart sounds were faint. There was no evidence of peripheral edema. Reflexes showed the prolonged contraction considered by Chaney¹² as pathognomonic of myxedema.

The basal metabolic rate was minus 30, the blood cholesterol 310 mg per 100 c.c., the urine normal, and the blood Wassermann test negative. The blood contained 3,270,000 red blood cells per cu. mm. and 8.8 grams of hemoglobin per 100 c.c. The sugar tolerance curve was normal, possibly slightly high, as the peak was at 176. Roentgen-ray showed the heart to be of normal size and appearance. The electrocardiogram revealed a low voltage of all complexes in all leads, the T-wave in Lead II was iso-electric.

Desiccated thyroid, one-half grain daily, was started and the dose was gradually increased to two grains daily. On this dose the basal metabolic rate became and remained normal (minus 7 to plus 9) and the blood cholesterol fell to 173 mg per 100 c.c. The heart showed no significant change in size. The voltage of the T-wave in Lead II became one mm. and the voltage of the other complexes increased slightly. The change in the patient's condition was the remarkable one usually seen in these cases, she felt well and had very few complaints. On 4/4/35, five months after starting thyroid therapy, the hemoglobin was still 8.8 grams per 100 c.c. in spite of the improvement in the other signs and symptoms. Iron by mouth was started and on 6/7/35 the hemoglobin had increased to 13.7 grams per 100 c.c. Figure 5 shows the change in the Achilles tendon reflex which occurred under treatment.

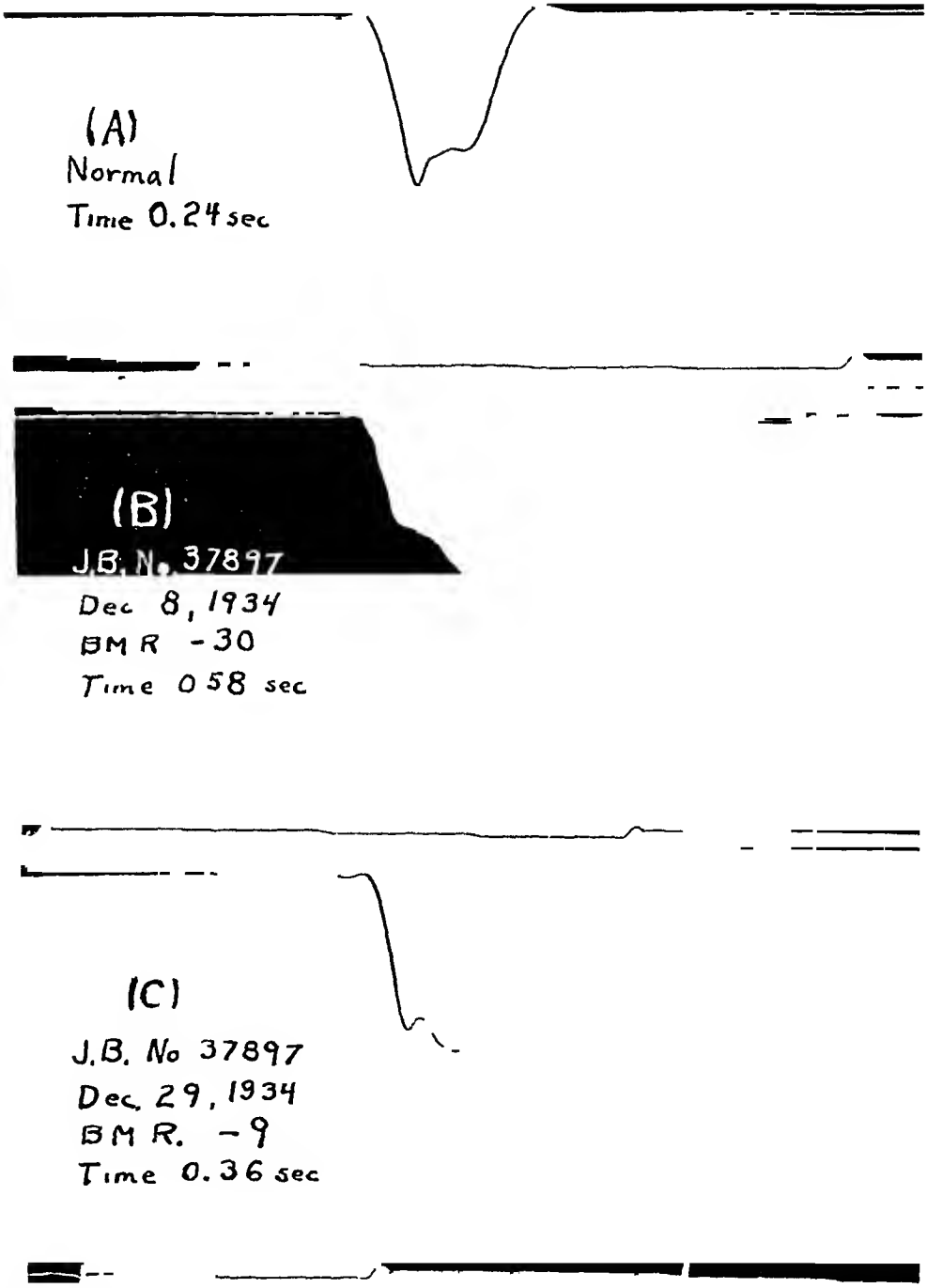


FIG 5 Case 4 Prolongation of the Achilles reflex in the myxedematous state (B) and shortening after thyroid therapy (C) A normal record (A) is presented for comparison

Note (1) The presence of a mental activity such as one might expect in hyperthyroidism persisting after the physical and laboratory signs of myxedema had developed. It is, of course, probable that the patient was mentally retarded in comparison to her previous hyperthyroid state, she still showed, however, a mental reactivity out of all proportion to her hypothyroid state. (2) The presence of low voltage in the electrocardiogram with a heart of normal size. (3) The most notable change in the electrocardiogram after therapy was increase in the voltage of the T-wave in Lead II. (4) The failure of the rather marked anemia to respond to thyroid therapy and the good response when iron was given. (5) The presence of the prolonged reflex as noted especially in the Achilles tendon reflex.

Case 5 Spontaneous myxedema in a woman, aged 51, with an interesting family history of diabetes

M. M., a white woman, aged 51, entered the clinic on 12/18/34 with numerous complaints, including the usual ones of fatigue, shortness of breath, inability to tolerate cold, poor appetite, constipation and slow mentation. Examination revealed the common signs of myxedema. The basal metabolic rate was minus 38, the blood cholesterol 283 mg per 100 c.c., the blood Wassermann test negative. Urine was normal except for a small number of pus cells. The blood count showed 3,800,000 red blood cells per cu. mm. and 12.5 grams of hemoglobin per 100 c.c. The sugar tolerance curve was normal. The gastric test meal showed no free hydrochloric acid and a total acidity of eight degrees. Roentgen-ray revealed a normal sized heart. In the electrocardiogram inverted T-waves in all leads, low voltage, and a slight left axis deviation were present.

Three grains of desiccated thyroid daily were required to keep the basal metabolic rate within normal limits. Laboratory tests six months after starting treatment were as follows: Red blood count 4,250,000 cells per cu. mm., hemoglobin 14.5 grams per 100 c.c., blood cholesterol 167 mg per 100 c.c., sugar tolerance normal—the curve was somewhat flatter than before treatment, gastric test meal unchanged. Heart size was unchanged. The electrocardiogram had become normal with an increase in voltage of the QRS complexes, upright T-waves in all leads, and no axis deviation.

Of special interest in this case is the family history. A sister died of diabetes. A son died in diabetic coma. A daughter has diabetes and congenital heart disease.

DISCUSSION

Terminology The term myxedema was applied by Ord,¹ in 1880, to the syndrome of "adult cretinism." As is common in other diseases, the outstanding or unusual characteristic of the disease was used as a name for the entire condition. When we speak, therefore, of an individual having myxedema, we refer to the entire syndrome—the slowed mental and physical processes, the dry skin, the brittle nails, the elevated blood cholesterol, the changed protein and mineral metabolism, and the other recognized changes—not to the single feature of myxedematous infiltration of the tissues. Since decrease or absence of thyroid secretion produces the state of myxedema in all of its features, we must consider myxedema as a manifestation of diminished thyroid secretion. Hypothyroidism, and myxedema are, therefore, synonymous terms. To speak of hypothyroidism without myx-

edema, as is occasionally done, is incorrect unless the term myxedema is used in its restricted sense, in which case one could also speak of myxedema without myxedema, using the term first as the name of a clinical entity and then as a description of a specific pathological condition. The expression "hypothyroidism without myxedema" is usually misused in reference to mild cases of myxedema, or, more frequently, to cases of hypometabolism. Myxedema and hypothyroidism imply more than hypometabolism and should not be used in the absence of other evidences of diminished thyroid function.

Symptomatology When it is recalled that the symptoms of myxedema are all produced by the absence of one hormone and entirely alleviated when that hormone is replaced, it is not surprising that a striking similarity is usually noted in the histories of cases of myxedema. Variations are to be expected in degree rather than in kind. Furthermore, it is unlikely that one symptom or sign would occur without the others being present in about equal degree. If, as recent experience indicates, normal cholesterol metabolism is closely dependent on the presence of a normal amount of thyroxin, we would not expect a markedly lowered basal metabolic rate due to lack of thyroxin without some evidence of altered cholesterol metabolism. The same reasoning applies to the other changes. The occasionally noted variations from this conclusion may possibly be explained in three ways. First, our normal standards for any one sign or symptom are averages from which marked variations must occur and what may, therefore, appear to be normal by our standards may really be abnormal for a specific individual, or vice versa. Second, it is possible that variation may occur at times in the susceptibility of a certain tissue to thyroxin, the tissue may develop an increased sensitivity or an increased refractility to thyroxin. Third, one or more of the signs of diminished thyroid secretion may be concealed by the presence of another pathological condition affecting the same signs in an opposite manner.

Means and Richardson² print a table compiled by Krantz showing the incidence of various signs and symptoms, table 1 is in great part derived from that table and shows in outline those symptoms which occur in the majority of cases. Experience indicates that the symptoms of myxedema develop slowly over a period of months and years. Menorrhagia is frequently seen in women in whom myxedema occurs before menopause.³ M. S. (Case 2) had two uterine curettements with little relief for a symptom that responded readily to thyroid therapy. J. B. (Case 4) illustrates a condition occasionally seen in patients with postoperative myxedema. Although most of the signs and symptoms of myxedema were present—lowered basal metabolic rate, elevated blood cholesterol, dry pasty skin, inability to stand cold, and fatigue—the mental processes were not slowed and were, indeed, more of the type which one might expect with her previous state of exophthalmic goiter. Thyroid medication produced marked improvement. Since her reactivity had always been normal or increased, very little change was noted in this feature, one did, however, feel that her speech and actions were more relevant and consistent than they had been previously.

TABLE I
Myxedema
Symptoms and Findings

<i>General</i>		<i>Edema</i>	
(1) Fatigue		(1) Eyelids	
(2) Weakness		(2) Face—checks	
(3) Inability to stand cold		(3) Ankles	
(4) Weight increase		Non-pitting	
(5) Fat increase		Pitting	
General		<i>Mental and Neurological</i>	
Supraclavicular		(1) Drowsiness	
<i>Skin</i>		(2) Slow speech	
(1) Paleness		(3) Numbness and tingling	
(2) Dryness and scalliness		(4) Impairment of memory	
(3) Absence of sweating		(5) Impairment of hearing	
(4) Hair—Scanty		(6) Prolongation of tendon reflexes	
Coarse		<i>Gastrointestinal</i>	
(5) Nails brittle		(1) Constipation	
<i>Circulatory</i>		(2) Poor appetite	
(1) Shortness of breath		(3) Indigestion	
(2) Slow pulse		<i>Blood</i>	
(3) Small pulse pressure		(1) Increased cholesterol	
(4) Poor quality of heart sounds		(2) Moderate anemia	
(5) Dilation of heart		<i>Lowered Basal Metabolic Rate</i>	
(6) Electrocardiographic changes			
Low voltage, especially in T-			
waves in Leads I and II			

Perhaps in this case the nervous system had been so sensitized that it responded to smaller amounts of thyroxin than the other tissues

The presence of "circumscribed myxedema" in cases of hyperthyroidism has recently been receiving some attention⁴ and presents an interesting paradox. Perhaps the explanation is in terms of development of decreased sensitivity to thyroxin in a limited area.

Basal Metabolic Rate The lowered basal metabolic rate is certainly of great importance in the diagnosis of myxedema. It must be emphasized, however, that a low basal metabolic rate is not of itself an absolute indication that hypothyroidism is present. Many individuals have a basal metabolic rate well within the myxedema range and have no myxedema. The low rate may represent their normal, or some factor other than lack of thyroxin may cause the lowered metabolism.

When the basal metabolic rate falls below minus 20, patients with myxedema usually begin to show mild symptoms—sensitivity to cold, dryness of skin, absence of sweating, but they do not develop the marked symptoms—swelling, mental retardation, cardiovascular changes—until the basal metabolic rate has been below minus 30 for some time.³ The question of whether symptoms of myxedema can occur with a normal basal metabolic rate is often raised. Patients are occasionally seen who have normal basal metabolic rates and who present symptoms which might be of myxedematous origin and which appear to respond to thyroid. One such case was seen recently in which there was also a somewhat elevated blood cholesterol. When we recall that the basal metabolic rate is influenced by factors other

than thyroid, the possibility of a myxedematous individual with a normal basal metabolic rate would appear to exist. Those cases in which the basal metabolic rate is elevated because true basal conditions were not obtained during the test do not belong in this category but should not be forgotten. An individual whose normal basal metabolic rate is plus 20 or more might show signs of hypothyroidism with a normal basal metabolic rate. A myxedematous individual taking dinitro-ortho-cresol⁵ would be an excellent example of a case of myxedema with a normal or even elevated basal metabolic rate. Whether cases might exist in which some substance similar to dinitro-ortho-cresol would be produced spontaneously in an individual having myxedema, thus fulfilling the above conditions, remains for the future to decide.

Blood Cholesterol Although it has long been known that changes in cholesterol metabolism are associated with thyroid dysfunction, the importance of these changes has only been recognized in recent years. Investigations have shown that the blood cholesterol is usually diminished in hyperthyroidism and almost invariably elevated in hypothyroidism. So consistent is this elevation of the blood cholesterol in myxedema that it has been suggested that the three criteria for the diagnosis of myxedema be (1) the presence of the characteristic symptoms and physical findings, (2) a lowered basal metabolic rate, and (3) an elevated blood cholesterol. To these might be added a fourth, return of the above three to normal under thyroid therapy. It has been pointed out that the efficacy of treatment can usually be predicted on the basis of whether or not the blood cholesterol is elevated. Those cases which have low basal metabolic rates and no signs of myxedema rarely show elevated blood cholesterol and are rarely benefited by thyroid therapy. Hurxthal⁶ believes that the finding of hypercholesteremia, in the absence of its few other common causes, points more specifically to thyroid deficiency than does the finding of a low metabolic rate. Determination of blood cholesterol has attained such importance that it may be said that no report of a case of hypothyroidism is complete unless the blood cholesterol value is given. It is interesting to note that in Case 2 the blood cholesterol before treatment, 236 mg per 100 c c, might possibly have been considered a high normal. After treatment, however, it fell to 137 mg per 100 c c, showing that the initial value represented an increase of more than 70 per cent over the normal value and again emphasizing the importance of variations in normal as an explanation of unexpected findings.

Recent studies of creatinuria in children with hypothyroidism require comment. Until about the age of puberty creatine is normally found in the urine of children of both sexes. In hypothyroidism in children the creatine excretion may diminish or cease entirely. With proper administration of thyroid creatine again appears in the urine.⁷

Carbohydrate Metabolism A consistent feature of experimental and clinical studies on carbohydrate metabolism is the lack of agreement between

the results of various workers. Several factors probably account for this poorly controlled experiments, conclusions drawn from too small a number of experiments, and the presence of only a small correlation between the two conditions. The conclusion that in myxedema the tolerance for carbohydrate is increased appears to be commonly accepted in recent literature but cannot be drawn with assurance from the results of experiments on animals ^{8,9}. The same is true of work on patients with myxedema without any evidence of diabetes, low blood sugars, normal blood sugars, low prolonged sugar tolerance curves, high prolonged sugar tolerance curves, and other types of curves have been reported. A glaring fault in many of these reports is the small number of cases. Some recent well controlled experiments ¹⁰ on hypothyroidism induced by total thyroidectomy indicate that carbohydrate metabolism is not significantly influenced by the hypothyroidism following total thyroidectomy. The belief that the tolerance for carbohydrate is increased in myxedema would appear to rest on two factors: first, it is well recognized that the sugar tolerance is diminished in hyperthyroidism and one would expect it to be increased in hypothyroidism, second, rather definite evidence exists that when diabetes mellitus and myxedema occur in the same individual, the diabetes becomes more severe as the myxedema is treated. It is believed that the decreased severity of the diabetes in myxedema results from the lowered metabolism and does not indicate any antagonism between the secretions of the thyroid and the pancreas. The lack of agreement concerning the effect of hypothyroidism on patients without evidence of diabetes, and the general agreement concerning the mitigating effects of hypothyroidism on diabetes may possibly be correlated as follows. The effect of hypothyroidism, or possibly lowered basal metabolic rate only, is not great enough to be detected by a rather crude test such as the sugar tolerance test because of the great reserve present in the carbohydrate metabolism. When, however, this reserve is lost, as in diabetes, the effect becomes evident.

Shepardson and Wever ¹¹ came to the conclusion, from a review of the literature "that the coincidence of diabetes mellitus and myxedema is probably no more nor less common than could be predicted from the occurrence of the two diseases separately." They also concluded that only 13 cases of diabetes combined with myxedema have been reported in literature. The actual number must be much greater. The family history of diabetes in two of the above cases (Cases 1 and 5) is very interesting. Case 1 is the only one that presented an abnormal sugar tolerance curve. She showed diminished tolerance which was somewhat further diminished by thyroid therapy but not beyond the limits of error of the test.

Change in Reflexes In 1924 Chaney ¹² described the abnormally prolonged character of the tendon reflexes in myxedema. On striking the tendon, the muscle contracts about as rapidly as normally, but remains contracted for as long as a second and relaxes slowly. Chaney apparently

obtained this prolongation in all of his cases of myxedema and considered it to be specific for myxedema since it did not occur in other conditions associated with lowered basal metabolic rates. Although this prolongation of the reflex is very striking and characteristic, it certainly is not always present. Case 1 did not show it or at least did not show it to an extent to be clinically observable. Case 3 showed it at times and at other times gave a quite rapid and normal reflex. When the prolonged reflex is present, it returns to normal with the basal metabolic rate. Figure 5 shows the nature of the reflex as obtained in Case 4 and the improvement with therapy. The prolonged reflex is an interesting sign which may, at times, be of help in diagnosis, but too much importance must not be attributed to its absence.

Blood and Urine The moderate degree of anemia which occurs in most cases of myxedema has been attributed to the diminished activity which the blood forming tissues share with all the other tissues. It must be remembered, however, that the pastiness of the skin in myxedema is out of all proportion to the degree of anemia, which may be very mild. Some improvement of the blood count and hemoglobin occurs with thyroid treatment but it has been my experience that iron therapy must often be used to bring the blood up to a full normal. In spite of remarkable improvement in all other ways in Case 4, a fairly marked anemia did not respond to thyroid but responded almost immediately to iron.

The urine is usually normal and was so in all of the above cases. However, traces of albumin do occur at times and are of interest only from the standpoint of diagnosis since, as in Case 3, these patients are frequently diagnosed as nephritics.

Gastric Acidity In spite of some observations to the contrary, the bulk of evidence appears to indicate that there is a definite decrease in gastric acidity in both hyperthyroidism and myxedema.¹³ Even more definite is the increase in incidence of achlorhydria in myxedema and a few observations¹⁴ indicate that this achlorhydria is not influenced by treatment (Cases 1 and 5). Interpretation of these findings, should further study confirm them, is difficult.

Cardiovascular Changes Zondek¹⁵ in 1918 used the term "myxedema heart" to describe a condition found in some cases of myxedema and characterized by an enlarged heart, sluggish cardiac movements and certain electrocardiographic changes. Although "myxedema heart" was at first thought to occur only rarely, recent literature contains ample evidence that it is a common and possibly the usual finding in myxedema. Lerman, Clark and Means¹⁶ believe that "the heart is generally enlarged in myxedema." The incidence of recognition of cardiac enlargement increases with greater care in examination and more frequent use of roentgen-rays. The enlargement, at times quite marked (Case 1), usually involves both sides of the heart. Digitalis has very little influence on the size of the heart, but thyroid therapy decreases the size. The changes which occurred in Case 1 are

shown in figure 1, the small amount of thyroid given in this case (one-half grain daily) is noteworthy. In some cases the heart will decrease in size after thyroid therapy even though it was apparently normal in size before treatment (Case 3). If thyroid is stopped, the heart enlarges, it shrinks again on resumption of thyroid (Case 2, figure 2).

Does the increased heart shadow mean hypertrophy, dilatation, or increased pericardial fluid? The rapid and, in many cases, great decrease in heart size appears to rule out hypertrophy as the entire explanation. Interstitial and intracellular edema, described below, might increase the size somewhat but hardly enough to account for the extent of enlargement which occurs in many cases. Reports of myxedematous patients showing pericardial effusion^{17, 18} and especially a case to be reported by Waring, emphasize the part which pericardial effusion may play in some cases. Lerman, Clark and Means¹⁹ feel that "in most cases, however, neither the clinical findings nor the roentgen-ray picture of the heart are consistent with significant amounts of pericardial fluid." We must conclude then that the increase in heart shadow is usually due to cardiac dilatation.

In spite of several earlier reports to the contrary, recent studies indicate that patients with myxedema almost invariably show typical abnormalities in the electrocardiogram and that these changes are favorably influenced by thyroid therapy. They occur even when cardiac enlargement is not present (Cases 4 and 5) and may be considered as early evidences of those alterations in the heart muscle which later may produce dilatation. Flattening or inversion of the T-wave in Lead II is considered the most characteristic change, but flattening of the other T-waves and general low voltage of all complexes in all leads also usually occur. Various other findings have been reported but not as constantly as the above. Many of these changes are illustrated in the cases here reported, all of which showed definite deviations from the normal in the electrocardiogram. These abnormalities usually disappear under thyroid treatment.

If we look for an explanation of the dilatation of the heart, we find that the cardiovascular changes which occur in myxedema can, for the most part, be divided into two groups: (1) those diminishing the circulatory load, and (2) those diminishing the strength of the cardiac contraction. In the former group belong the decreased blood volume and cardiac output. In the latter belong the pathological changes in the heart and blood vessels, the diminished coronary circulation and, possibly, the loss of the tonic effect of thyroxin on the heart muscle. The mild anemia which is often present would be another factor decreasing the cardiac efficiency.

The cardiac minute volume output is markedly diminished in hypothyroidism¹⁹ in the absence of cardiac insufficiency. Of major importance in producing this diminished cardiac output is the decreased blood volume.^{20, 21} Thompson²⁰ calculated that the increase in total blood volume on administration of thyroid to cases of myxedema was not infrequently as

much as 25 per cent. The relationship between the cardiac output and the blood volume is evident in the observation that other conditions remaining the same, the cardiac output varies directly with the volume of circulating blood ²². As pointed out below other factors are probably also involved in the production of the diminished cardiac output.

Of the factors decreasing cardiac efficiency, the pathological changes in the heart muscle must be most important. Exact information is lacking concerning the nature of these changes because of the dearth of autopsy material on untreated cases and because of our inability to distinguish between those changes due to myxedema and those due to commonly associated conditions most important of which is arteriosclerosis. Experimental work in animals must be interpreted with caution. Changes due to myxedema can be divided into those that are reversible, that is, disappear on giving thyroid, and those that are irreversible. Possible reversible changes in the myocardium are (a) interstitial edema, (b) intracellular edema, and (c) a moderate degree of granular degeneration. Among the irreversible changes is the degeneration of the muscle fibers described by Webster and Cooke ²³ and others. The changes produced by such complicating factors as arteriosclerosis and hypertension and exemplified by coronary sclerosis and myocardial fibrosis are of course irreversible.

Although it appears to be generally assumed that the coronary blood flow in myxedema is decreased, attempts to analyze the possible changes in the light of modern conceptions of the mechanics of coronary flow would seem inconclusive. In a denervated heart preparation, the mean pressure in the aorta appears to be the most important factor determining coronary blood flow ²⁴. Since in myxedema the diastolic pressure is usually increased and the systolic pressure very often somewhat increased, if blood pressure were the only factor, coronary blood flow might also be increased. In the intact heart preparation, however, a reflex nervous mechanism apparently keeps the coronary blood flow proportional to the cardiac output ²⁴. Since the cardiac output is greatly decreased in myxedema, a diminished coronary flow is to be expected. The influence of other factors, such as, rate and strength of contraction, and muscular tone cannot be properly measured in our present state of knowledge. Essex and his co-workers ²⁵ state that thyroxin augments the coronary flow as much as 300 to 400 per cent over the control values. The extent of the increase is so great that it would appear that some specific effect might be involved. Since decrease in cardiac output is the most marked change and since this decreases coronary flow it is probable that the final effect is a diminished coronary blood flow.

Yater ²⁶ and others have shown that thyroxin stimulates the heart muscle producing an increase in heart rate. It is quite possible, although not proved, that it may also exert a tonic action on the heart. Yater advances the hypothesis that the increased circulatory output in hyperthyroidism is not a result of the increased need of the tissues for oxygen but a fortuitous

circumstance resulting from the stimulation of the heart by thyroxin. Without entering upon a critical analysis of the theory, we may advance the corollary in regard to myxedema. The diminished circulation in myxedema would thus be considered, not as an adjustment of the circulation to a diminished oxygen need, but a fortuitous condition arising from the lack of thyroxin to stimulate the heart. The decreased blood volume, described above, and the poor venous return resulting from the diminished muscular activity and lowered skeletal muscle tone would further lower the cardiac output. In favor of this hypothesis is the lack of correlation between the lowered basal metabolic rate and the decrease in cardiac output¹⁰; the cardiac output is decreased more than would be expected and an increase in the arterio-venous oxygen difference is produced.

The incidence of hypertension seems to be greater in patients with myxedema than in the general population^{16, 17}. On treatment the fall of blood pressure in those patients showing hypertension is apt to be marked and in a large proportion it returns to normal. Occasionally a patient showing a normal blood pressure before treatment may become hypertensive under thyroid therapy. Although hypertension when present means an added load on the heart, the possibility that it may represent a compensatory mechanism must not be forgotten.

Having examined the changes which increase and also those which decrease the load of the heart, we may follow Hallock²⁸ in his explanation of the dilatation of the heart. The pathological changes in the muscle, the diminished coronary circulation, the loss of the tonic action of the thyroxin, and the mild anemia tend to diminish the strength of the cardiac contraction—to make the heart hypotonic. Although the diminished blood volume and circulatory output decrease the work of the heart, in some cases they do not balance the harmful factors and the heart cannot carry on its work without in some way increasing the strength of its contractions. This it can do by increasing its diastolic size since according to Starling's "law of the heart" the greater the initial length of the muscle fibers, that is, the greater the diastolic size of the heart, the greater the force of contraction. The heart, therefore, increases its diastolic size.

We must leave Hallock at this point to consider another phase of the problem, the relation of venous pressure to cardiac dilatation. Increased venous pressure is the price that the heart usually pays for the increase in size which permits it to contract more strongly. This will be made more evident if we examine Harrison's concept of the cause of increased venous pressure in the pulmonary circuit²⁹. If the left ventricle is working against a load (or if, for any reason, it cannot contract as efficiently as previously) it does not expell the usual quantity of blood. Since it is still receiving the same amount, the blood collects in the ventricle and its diastolic size increases. With increase in size, its strength of contraction increases and it now expells its original amount. As the left ventricle dilates, however,

the pressure in it rises a little toward the end of diastole and the left auricle, now working against this greater pressure, fails to empty itself completely and blood collects in it until, in spite of its distensibility, the pressure increases. As a result of this increase in pressure in the auricle, less blood enters the auricle than formerly. Since the right ventricle is still expelling the same amount, the blood accumulates in the lungs and the pressure in the pulmonary circuit increases. This rise in pressure now corresponds in degree to the increase in the pressure in the left auricle. It can thus be seen that the origin of the increase in venous pressure in the pulmonary circuit (pulmonary congestion) is in the resistance of the muscle fibers of the left ventricle to stretching. If in the foregoing illustration the muscle fibers of the ventricle could have stretched without requiring an increase in the pressure in the ventricle toward the end of diastole, there would have been no need for increase in pressure in the auricle and no resulting pulmonary congestion. The factor involved might thus be considered a sort of "stretching resistance" of the muscle fibers, or a "filling resistance" of the heart. This resistance to stretching may depend upon a sustained partial contraction of the fibers (muscle tonus) or upon the elastic properties of the fibers and would vary with changes in either. Because of this "filling resistance," dilated hearts, beyond a certain degree, are ordinarily accompanied by signs of congestion, that is, signs of increased pulmonary or systemic venous pressure. If, then, the "filling resistance" is normal in myxedema we would expect to find congestive signs with moderately or greatly dilated hearts.

Congestion in the pulmonary system would be evidenced by diminished vital capacity, dyspnea, orthopnea, increased pulmonic second sound, basal râles, and cough. Vital capacity studies have not as yet been complete enough to give definite evidence for or against the presence of congestive failure in most cases. The observation²¹ that the vital capacity was strikingly diminished in myxedema in the absence of any signs of congestive heart failure, and did not show significant changes following treatment makes any interpretation of vital capacity studies difficult. Dyspnea is one of the earliest evidences of congestive failure but as it can be produced by other causes it cannot by itself be considered as absolute evidence of congestive failure. Its frequency in myxedema may be otherwise explained. Of primary consideration is the patient's frequent confusion of shortness of breath and fatigue. The latter is a marked and universal symptom in myxedema and close questioning will often reveal that what was considered shortness of breath is really fatigue. With diminished blood volume, and with inadequate venous return as a result of poor muscle tone and diminished and poor contraction of the skeletal musculature, it is possible to have dyspnea on the basis of inability to increase cardiac output from a form of peripheral failure. Orthopnea is only rarely described as a symptom in myxedema. The pulmonic second has not been mentioned as accentuated

Basal râles and cough are occasionally present but usually no more frequently than might be expected from causes other than congestive failure.

Evidences of increased systemic venous pressure are indicated by distended cervical veins, increased venous pressure measurements, peripheral edema, and enlarged liver. Distended cervical veins are only occasionally noted in the literature. They were not seen in Cases 1 and 2 above. Where reports of venous pressure measurements are mentioned they have usually been normal. The work has, however, been done in most cases on patients with normal sized hearts and with no signs of venous congestion. Altschule and Volk¹⁹ found that the venous pressure remained normal in three cases of postoperative myxedema in which the heart enlarged with development of the hypothyroid state. Pitting edema around the ankles occurs in a large percentage of the cases of myxedema including many cases with hearts of normal size. Since edema on a cardiac basis does not occur, with rare exceptions, unless the heart is dilated, we must assume that in most cases of myxedema the edema is on a non-cardiac basis. Edema, when present, may be on the basis of local circulatory changes such as poor venous return due to poor muscle contraction and tone, on interference with venous return due to fatty and possibly myxedematous deposits, and on local tissue changes. The presence of an enlarged liver which diminishes in size after treatment is occasionally reported.

It can thus be seen that in only a small percentage of the cases of myxedema with cardiac enlargement can the signs and symptoms be considered as conclusive evidence for the presence of congestive heart failure and that in most cases one need not assume the presence of congestive failure. We have then a condition in which the heart is dilated, often greatly, and it has done so without paying the price of increased venous pressure, in other words, the "filling resistance" is decreased. This may possibly result from a loss of the tonic effect of thyroxin or from changes in the elastic properties of the muscle fibers produced by the absence of thyroxin. Even more definite evidence of this decrease in the "filling resistance" may be found in cases of congestive failure treated by total ablation of the thyroid. In some of these cases improvement, decrease or clearing up of the symptoms of congestive failure, may occur even though the heart continues to dilate³⁰ that is, the same or a greater degree of dilatation may be present with a lower venous pressure. The improvement in these cases is usually ascribed to the diminished demand on the heart which results from the lowered metabolism. Although the importance of this factor is evident, it does not explain how the heart can maintain the same size or even become larger while the venous pressure decreases. The heart in these cases must have less "filling resistance," permitting dilatation with a smaller venous pressure. If by the induction of hypothyroidism in these cases of circulatory failure, the circulatory load is diminished and the heart permitted to maintain its same size with a lower venous pressure (thus giving it the advantage of increased

diastolic length), and if the pathological changes resulting from hypothyroidism are kept at a minimum by not permitting too low a basal metabolic rate, the improvement often seen can easily be explained.

The foregoing discussion may be summarized as follows. The changes in the heart produced by lack of thyroid tend to make the heart hypotonic. At the same time changes occur in the muscle fibers which permit them to stretch more easily and give the heart a diminished "filling resistance." If the hypotonicity is great enough to require a greater initial length of the muscle fibers to produce an adequate contraction, the heart dilates, but since the "filling resistance" is diminished it does so without increase in venous pressure and without congestive changes. If pathological changes, such as arteriosclerosis, hypertension, or rheumatic heart disease are present, congestive failure may occur either because the dilatation is sufficient to produce increased venous pressure in spite of the lower "filling resistance," or because the "filling resistance" cannot diminish as much in an hypertrophied or fibrotic heart as it does in a normal heart.

On treatment with thyroid, various results might be expected. If the pathological changes are reversible, the heart size may decrease as a result of the improvement in tonus. If the pathological changes cannot be reversed by thyroid, the individual may become worse since the "filling resistance" and the circulatory load are increased, congestive failure may result or become aggravated. In some cases the factors may balance and the condition remain the same.

TREATMENT

Many cases of myxedema are quite sensitive to thyroid and only small doses are needed to produce marked changes. This is very nicely illustrated in Case 1. It has been said that the more thyroid an individual can tolerate, the less hypothyroid he is. In view of the marked cardiac changes which are frequently present, the necessity of increasing the basal metabolic rate gradually and permitting the heart to adjust itself to the changed load is obvious.

Various brands of thyroid contain different amounts of iodine and show some variation in strength. Furthermore, some firms label tablets according to the amount of fresh gland present and others according to the amount of dried gland present. Since one part of dried gland is equivalent to about five parts of fresh gland, this difference must be remembered, for example, a five grain B. W. and Co. tablet is approximately equal to a one grain Lilly tablet.

Finally, since "the effects (of thyroxin) start only a day after administration, even with intravenous injection, and then continue to increase, reaching their maximum in about 10 days, after a single dose,³¹" it is useless to give thyroid in broken doses during the day.

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INFANTILE CEREBRAL PALSY, ITS TREATMENT BY SELECTIVE INHIBITION OF SENSORY STIMULI

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WHEN the nervous system has been damaged by disease or injury at birth and choreo-athetosis, spasticity, ataxia or some other type of hyperkinesia is present, the tendency in prescribing treatment is to place too much emphasis on physical training without due consideration of the effect that repetition of an activity has upon the growth of the behavior pattern at various stages of development. Stepping movements, for example, show themselves almost immediately at birth but no amount of exercise is going to enable the normal infant to walk until his nervous system has attained adequate differentiation. In the case of the cerebral palsies there are also limits circumscribed by anatomical and physiological growth beyond which no amount of exercise will help the patient and in fact the overdoing of such exercise may even lead to greater difficulties, as for instance, in the case of the mother who ties up the good hand of the hemiplegic child thinking that the more he uses the maimed member the sooner it will be normal. She often creates speech disorders and behavior difficulties which are far more serious than the original handicap. Now and then one comes across a spastic whose physical training has been almost negligible, who becomes an author, a teacher, an attorney, a librarian or a successful business man in the face of what seem to be insurmountable difficulties, while another spastic whose physical affliction is slight in comparison and who possesses average intelligence becomes anti-social in spite of having had supposedly the best of muscle training, all of which makes one feel that the more important part of treatment has been neglected, namely that of developing the assets which the child already has at his disposal and aiding him in adjusting to his handicap and the conditions of life as he finds them. As the child develops the unimpaired areas of his brain and acquires outside interests, there is a corresponding improvement in muscle control, as is exemplified in the case of the spastic girl who is so muscle conscious during meals that she cannot feed herself but nevertheless is able to forget herself in music to the extent that she plays the piano most satisfactorily. The fact that a spastic athetoid is able to maintain perfect control of his muscles when fear, anxiety and self-consciousness are in abeyance should be evidence enough that progress in the treatment of such conditions does not rest in exercises which will make the patient all the more muscle or speech conscious but rather in applying measures that will tend to reduce to a minimum the number of sensory stimuli to which the patient is unaccustomed to attending simul-

* Delivered in part before the General Sessions, American College of Physicians, Detroit, March 2, 1936

taneously In this paper I shall relate observations on the effect of sensory stimuli on muscular activity in cases of cerebral palsy

During sleep, when sensorial impressions are reduced to a minimum, the purposeless movements cease and the muscles invariably attain relaxation even in the worst cases of spasticity and athetosis Contrary to one's expectations, after a good night's sleep, the patient is usually worse during the morning hours A mother will relate that her child is unable to feed himself at breakfast but finds little or no difficulty with the evening meal The thought processes are also reflex activities and in the case of the spastic athetoid may be as hyperactive as the knee jerk His power of concentration is therefore limited, and is reflected in overflow motor activity, which grows less as the child gets into the routine of the day's play or work and the sensory stimuli, which his nervous system is unaccustomed to handling simultaneously, are lessened The value of an academic program in helping the spastic athetoid of good intelligence cannot therefore be overemphasized Parents who delay academic training until the child acquires better control of his hands or speech are surprised at the rapid improvement in muscle control which follows when the child is finally allowed to go to school

When the spastic athetoid emerges from a deep sleep to the waking state and is suddenly confronted with more sensory stimuli than his defective nervous system can adequately handle, we find a corresponding sudden change from a state of complete muscular relaxation to a state in which the patient exhibits his least ability to control muscular movements If the change from sleep to the waking state is more gradual, as for example during the recovery from the effects of ether anesthesia, the patient's ability to control his muscular movements will be at its best when he emerges from the ether and will become progressively worse as the effects of the ether wear off In taking histories of cases of choreo-athetosis with and without spasticity, it is a common experience to find that patients or their relatives volunteer that much of the choreo-athetosis and spasticity have been lost for a short time after recovery from ether anesthesia after surgical operations One mother related that the first time she had ever been able to understand the speech of her spastic athetoid and dysarthric child was when the child was recovering from the effects of ether following a tonsillectomy I have had occasion to witness a child under similar circumstances There was little or no dysarthria when the child was coming out of the effects of the ether As the ether wore off the child's words became less and less distinct and finally the speech became as dysarthric as before the operation

In an illustrated lecture before the American College of Physicians in 1936, I showed movies of the effects that alcohol had on controlling athetosis and spasticity in the case of a man of 45 years of age He was unable to bring a full glass of water to his lips without spilling half the contents After drinking two ounces of whisky he was able to handle a full glass of

water without difficulty. At no time during the alcohol experiment was any evidence present of impairment of intellectual processes, of dullness, stimulation, euphoria, or loquaciousness. The patient was not an addict to alcohol although he had been aware of its effects for many years. The subjective feelings of one such patient were interesting, his comment being "Alcohol does not necessarily make me do things better, but makes me forget the things which I do badly." Another comment was "My friends tell me that I am more drunk when I am sober than when I have had a drink."

The majority of observers have explained the origin of choreic and athetoid states on the basis of basal ganglia damage. There is reason, however, to speculate as to their possible cortical origin. Suffice it to say that the effects of alcohol are supposedly those of reducing the activity of the higher centers of the nervous system. Under the influence of alcohol, the lower centers (basal ganglia) retain a certain degree of autonomy and can carry on their functions without being influenced by the damaged cortex. It is difficult to explain the observations made unless one accepts the theory that alcohol diminishes the domination of the higher cortical structures over the dependent and phylogenetically older lower centers. Possibly the mechanism is an elevation of the sensory threshold by alcohol and a corresponding reduction of the number of sensory impulses reaching the higher centers.

If choreo-athetosis and spasticity can be abolished through administration of ether or alcohol, then other measures of cutting down sensory stimuli should be equally effective in controlling adventitious muscular movements. It must be emphasized, however, that these stimuli are not to be eliminated altogether but should be reduced to the minimum necessary for the production of a well coordinated motor act. In the case cited above of the athetoid child who spoke better when under the influence of ether, too much of the drug caused cessation of all activity and too little was without effect—but when the concentration of ether was such that sensory stimuli were depressed just enough, then the act of speaking was almost perfect.

McGraw made observations on the behavior of the normal infant who was just beginning to extend his arms to reach for an object in the visual field. She showed that if the sight of the object is excessively stimulating the energy which should be directed toward extension of the arm in the direction of the object becomes converted into disorganized general body activity. Too little interest in the object would fail to stimulate movement in the direction of the object and too much interest would interfere with the individual's control over the motor activity involved. It is desirable that the individual should be interested in the object just enough to elicit a well controlled motor act. McGraw found that if the child was allowed to handle the object before reaching for it and thereby increase his sensory

experience the excess motion in the reaching prehensile act would be eliminated

I made a related observation in the case of a spastic athetoid patient who was given blocks to pile up on a table. He placed the first one on the table with only slight athetosis. The placing of the second block on the first was done with an increased amount of overflow activity, which was further augmented when the third was placed on the second. The fourth could not be placed at all and the whole pile was knocked down. This was repeated several times with more or less the same results. The patient was then made to wear a pair of partially opaque glasses which cut down his vision to the blocks and the immediate vicinity of the table. He was then, after a few trials able to place one block on the other without as much overflow and was able to pile more blocks than before. One must not draw the conclusion from this that merely fitting a pair of dark glasses to such a patient is going to relieve him of all his athetosis, but it does show that in this particular case excess visual stimuli did play a considerable part in the production of overflow activity. I was impressed by the effect that cutting down visual stimuli had in enabling an athetoid young man to feed himself in the presence of others who were watching his grotesque muscular movements during a meal in a restaurant. The more apprehensive he became of the people watching him, the greater was his difficulty. Being very myopic, he removed his glasses and not being able to see the others as well as he did before, he finished the meal without any trouble.

In helping a spastic athetoid to use his hands, it is often surprising to find how a slight pull over a muscle or tendon (proprioceptive sense) will prevent an overflow of muscular activity and will enable the patient to maintain perfect control as long as we keep the pressure there. By means of using a small iron disc fastened with adhesive tape to the skin I have through the force from the electro magnet on that disc been able to study the effects of a pulling force on a particular muscle group. In a subsequent paper, I shall report these findings.

The spastic athetoid has difficulty in correlating muscular activity and perception. He tries to look in too many directions at once. In shaking hands he thrusts his hand out aimlessly. If before shaking hands he is asked to look sharply at the thumb of the hand he is trying to reach, he will have no difficulty in shaking hands. Speech is likewise improved when the spastic athetoid focuses his eyes at a certain point in speaking. This is one of the reasons why lip reading is valuable in helping the general type of dysarthria present in spastic athetoid cases. If the person has to read lips he will obviously have to look at the one whose lips he is reading and in so doing he cuts down his vision with a consequent decrease in adventitious muscular activity. In learning to walk, the patient looks in every direction except where he is walking. This was illustrated in an athetoid case with considerable ataxia. In attempts to walk, the patient would stagger along

like a drunkard not looking in the direction of his walking and holding his arms flexed at the elbow and wrist. When he was told to focus his eyes steadily at a point in the direction of his walking, the overflow movements ceased, his gait became better and the arms came down to his sides without the patient being told to bring his arms there. When this same patient had to walk in total darkness, he became terrified and could not take a single step without falling. One dark evening when this patient was walking outside in a pair of white shoes, I noticed that his gait was better than I had ever seen it on previous occasions. The darkness of the night in cutting down his vision to the white shoes and the road, eliminated excessive motor activity. Here we have a child who is hardly able to walk in full daylight, is not able to walk at all in total darkness and yet, is capable of obtaining an almost normal gait when the visual stimuli are cut down to the proper amount.

According to McGraw the origin of many childhood "fears" may be attributed not necessarily to some unpleasant experience and its resultant associations but to a natural growth imbalance or lack of integration between several aspects of development. A child walking in the dark will show muscular tensions if his perceptive development is at such a stage that it does not integrate smoothly with the motor adjustments involved. This attitude may persist until it constitutes a "fear" of the dark. If the child's experiences are treated casually, the tension resulting from normal growth imbalance will soon fade except to the extent that a degree of tension may be needed for handling the situation. If a natural growth imbalance contributes to the development of an attitude of fear in the normal child, how much more should not such a factor be responsible for producing a similar attitude in cases of cerebral palsy where disease or injury is primarily responsible for growth imbalance.

Studies by Brickner and Lyons on individual acquired automatic associated movements in cases of encephalitis show that the organism remembers the acquired acts while instinctive acts are impaired. They cite as an example the case of a man who was a star pitcher for the New York Giants until six years before when he contracted definite and typical epidemic encephalitis. He is able to walk only with difficulty and all his routine motions are made with the usual retardation. In their test the man stood on the lawn of the hospital, his head and shoulders stooped, his hands trembling, his whole attitude one of characteristic rigidity and immobility. But when a ball was thrown to him, his whole body immediately became plastic, he made a perfect catch out at the side and at once threw the ball back. The whole act was characterized by a beauty and grace not attainable by the ordinary normal man. Brickner and Lyons state that "specific acquired acts in which grace and automaticity were achieved by the individual patient, prior to the onset of the illness can still be executed by patients with epidemic encephalitis despite rigidity."

In the introductory paragraph of this paper, the case of a spastic girl was mentioned, who is so muscle conscious at meal times that she is unable to feed herself, but is nevertheless able to forget herself in music to the extent that she plays the piano quite satisfactorily. Mention should also be made of a bacteriologist who has great difficulty in feeding himself but is nevertheless most successful at his profession. Still another case is that of a spastic athetoid whose difficulty is in feeding himself and yet he is able to play golf and compete with many normal men, in fact, his ability is so great that he might some day become a professional. The ability of the encephalitic to catch a ball in spite of rigidity and the ability of the congenital spastic athetoid to play the piano in spite of not being able to feed herself, suggest that the factor for the preservation of skilled acts in the case of the encephalitic must have something in common with the factor for acquiring a skilled act in the case of the spastic athetoid. This common factor is of interest.

The beginner at the piano may experience as much difficulty in placing the right finger on the right key as the spastic athetoid does in learning to handle a cup. Through practice the piano player learns to limit movement to certain muscles and eventually is able to play a well practised piece without much conscious effort. The difference between a normal person acquiring a skilled act, such as playing the piano, and the spastic athetoid learning to handle a cup is not so much a matter of complexity of muscular movement, as it is direction of attention upon the purpose of the act. The pianist is not interested in muscle training per se, but in a purpose, he wants to play and his muscular skill increases as he forgets himself in his music and learns to play without conscious effort. The hand of the spastic athetoid likewise becomes more agile as he forgets himself in his work. This is illustrated in the case of a chemistry student with a bilateral athetosis. He could hardly feed himself when he entered college. Through studying chemistry he developed considerable manual dexterity. When he started laboratory work, fear of acid burns made him spill solutions although he had no difficulty in handling two empty beakers. As he learned to pay more attention to the chemistry problem involved in his laboratory work, fear abated and manual control increased. The manual ability thus gained meant more to him than any amount of conscious muscle training he had ever undertaken.

The value of routine exercise cannot be determined by how well the spastic athetoid performs in the treatment room. I know spastics who perform splendidly in an environment to which they are accustomed but who go all to pieces when confronted with new situations. The spastic therefore needs something more than physical training to fortify him when he faces the new conditions of life and is confronted with more sensory stimuli than he can adequately take care of.

Merely to teach him to let go of his tense muscles by thinking of a rag

doll on such occasions is not going to solve his problem. Neither will ether, alcohol, luminal or other sedatives, in spite of their effects on cutting out sensory stimuli, yield any permanent results. The patient must develop the assets which are already at his disposal. As these assets are given opportunity to develop, the patient begins to feel that he is an integral part of society instead of an ostracized member. His greater assurance and confidence will make him more oblivious of his condition and less apprehensive of his shortcomings, all of which tend to minimize the sensorial input with a consequent increase in equanimity.

We are becoming more aware of the importance of vocational guidance and of the direction of the education of normal children towards equipping them to enjoy a full life. The value of providing the child with the means of manifesting its ability in one way or another has long been recognized. Why should we not have schools which, in addition to providing physical training, will be equipped also to enable the spastic to gratify in acceptable ways his desire for personal worth? The spastic athetoid who sits all day waiting for his next exercise and watching the activities of normal children cannot help but develop an attitude of anxiety or resort to daydreaming instead of the contemplation of reality. Such a child is helped by placing him with a group of handicapped children of average mentality assuming that his rating is such that he can learn to compete and develop a sense of importance.

The delay in the mental development in the spastic athetoid group is usually attributed to the lack of that type of mental growth which is stimulated by grasp and touch in every normal child. I feel that the reverse is truer, that is, the defect in muscular control is accounted for by the lack of a rounded education program for that child. The aim of such a program should be to develop objective interests which lead to the cutting down of sensory stimuli to those connected with the act that the patient is performing. The spastic athetoid cases mentioned above who have difficulty in feeding themselves and yet are able to do skilled acts satisfactorily like playing golf, playing the piano, and working out problems in chemistry and bacteriology behave in such fashion because such activities hold their interest whereas feeding is such a routine procedure that they are unable to develop interest in the act sufficiently to forget the things they do badly.

Between 15 and 20 per cent of crippled children are victims of intracranial hemorrhage. In some states the percentage is as high as thirty. It is maintained that nearly all of such cases develop serious behavior difficulties later in life. In the spastic athetoid group an estimate of the intelligence is often obscured by the muscular defects to the extent that they may be falsely regarded as completely defective in mentality or as possessing normal mental potentialities capable of development under physical training. It is pathetic enough to see a mother bring a mentally defective cripple to the clinic for physical training year in and year out in the hopes that as he gets

the use of his hands his intelligence will increase proportionately and will eventually approximate normal. But nothing is more heartbreaking than an intelligent child with a spastic arm or leg approaching adolescence who in spite of having had the best muscle training is rapidly becoming markedly introspective because of his inability to adjust to his handicap. In some instances the milder the physical affliction the more severe is the mental handicap. When faced with new situations, the spastic generally takes the easiest way out. In school the teachers are lenient with him and should he not know the answer required it does not take much effort to appear more nervous than usual and thus invariably the teacher refuses to press him, taking it for granted that he knows the answer.

I know one successful business man who completed high school in that way. He attributes his success not to his feigning in high school but to a strict master in college who would not let him hide his ignorance behind an exaggerated athetosis. The result was that he had to repeat his first year in college. He was given every opportunity to prove his worth. Extended time was allowed him in taking examinations but he had to learn to face reality. He had to recognize the fact that the things he had formerly been praised for—such as ability to bring a cup to his lips without spilling, an act expected of everybody without comment—did not constitute the things of major importance in life. The spastic is often made to feel that his main purpose in life is to live to get well, rather than to learn something that will compensate for his afflictions. Is it any wonder then that we read such sweeping statements to the effect that two-thirds of the cerebral palsies are mentally defective? And this refers not only to the severely handicapped, but as well to those so slightly motor handicapped that they cannot be called crippled.

In discussion of the latter group, it is often mentioned that they are unable to progress from the infantile stage. Intellectually function may be little impaired, while effectively these individuals show disturbance or even incapacity of judgment and practically behave as weak-minded. Their social adjustment is interfered with because of their proneness to an attitude of foolish cheerfulness, of nonsensical levity, or of lack of reserve, which their vain self-satisfaction accentuates. Such cases are probably much more frequent than would be noted merely from those who fall under clinical observation, since the physical affliction is so slight.

To dismiss this group and say that nothing can be done for them because their anti-social behavior can be explained by a slight intracranial hemorrhage is as absurd as thinking that the one armed man cannot adjust to his handicap and become a useful citizen. I have seen many such children become socially adjusted through placing them for a time with a physically handicapped group with whom they can learn to compete. Having once gained self-assurance and confidence that their inferiority can be adequately compensated for, they feel their worth is proved. This belief can then be carried over into other situations.

One striking example is the case of a boy of 12 years whose muscular handicap was so slight that it was noticeable only when he became embarrassed or had to face new situations. In school he did not get along well and was several grades behind his age. He complained of headaches and had to be excused from class several times a week. By placing this boy with a group of handicapped children of average intelligence where he was able to show them how to play ball and swim, it did not take long until he was up to the average class. What he gained at camp he was able to carry over most satisfactorily in a normal environment.

The problem of the cerebral palsy child, and this can also apply to the nervous child in general, is not going to be solved by establishing large hospital schools where hundreds of such cases can be taken care of. Such a child needs guidance in helping him meet new situations, and not institutionalization. There are adequate facilities in most of our larger cities for diagnosing and prescribing treatment for the birth injured but the prescription is one that cannot be filled in the corner drug store. The establishment of special schools running in conjunction with the local board of education where the mental and physical development can be simultaneously controlled will enable the child to receive the prescribed treatment. There should be a centralized hospital school for diagnostic and teaching purposes where parents and teachers can be instructed in handling these cases. Cases accepted for education and treatment in these schools should be selected according to the severity of the lesion, the age of the patient, the degree of the intellectual impairment, whether a progressive disorder or whether a hereditary affliction. This calls for not only careful clinical examination to detect the special disabilities but also careful analysis as to the intelligence rating. At times encephalogram studies and careful psychiatric and sociologic investigation are necessary.

Since the infantile cerebral palsies do not constitute a single disease with a single etiology, a detailed history is necessary to rule out the progressive types of disturbance which are not amenable to therapy. The severity of the lesion or the diagnosis of the condition in doubtful cases can be estimated frequently by the use of the encephalogram. This proved to be the case when identical twins with a history of instrumental delivery accompanied by cyanosis, a disturbance of gait, speech and general incoordination were presented for observation. Had only one twin survived, the conclusion would have been that the condition resulted from birth trauma but the evidence of identical twins with identical brain defects, which encephalograms revealed, made any other cause than failure of development impossible. Obstetrics is often unjustly blamed for producing many of these conditions. While we should manifest a greater concern to the ends of encouraging better prophylactic measures and after treatment, at the same time it is important to bear in mind that unless the factors contributing to the cause of the disturbance are more accurately ascertained, and no one is un-

justly blamed for producing the condition, we are not going to get the co-operation of physicians in stimulating interest in the establishment of schools where cases of infantile cerebral palsy can be properly trained. Neither must it be concluded that just because we make a diagnosis of birth injury we are dealing with a fixed type of brain injury. Dyke, Davidoff, and Masson have shown that a porencephaly due to trauma may cause a progressive type of disorder. A traumatized nervous system, on the other hand, is more susceptible to infections and not infrequently there may be a superimposed encephalitis. At adolescence the difficulties are sometimes accentuated because the patient then becomes more conscious of his affliction. Aside from the progressiveness or non-progressiveness of the disturbance a clinical examination should reveal what contributes to the status which the muscles are in. Is the atrophy one of disuse or has the lesion interfered with the nutritional centers of the brain? It is not only necessary to know whether the muscles are spastic, athetoid, ataxic, etc., but more important is to know the type of sensory stimuli which tends to keep them in that condition. We have mentioned the importance that visual stimuli play in learning to walk, to control the hands and in talking. It is often surprising to find that a patient who has never been able to walk will do so shortly after the surgical correction of a strabismus. I have also seen head shaking and other adventitious movements disappear after muscles necessary in controlling the eyes have been treated. Almost 15 per cent of the cerebral palsy cases which have come to my attention have definite impairment of hearing, sufficiently to interfere with their speech development and education. They are not deafmute, or aphasic. Just as color-blind persons are blind to one end of the spectrum, so others may be deaf to one end of the tonal scale. There are special methods for diagnosing and treating such conditions. Obviously if a person with cerebral palsy has a reading disability or educational difficulty he is not going to profit from the ordinary classroom routine, and special training in addition to his muscle therapy has to be devised. Care must therefore be exercised in differentiating between a special disability and a deficiency. The latter is not amenable to treatment, whereas a special disability, such as in speech and in reading and writing, can often be overcome under proper training.

The treatment of infantile cerebral palsy in contrast to that of anterior poliomyelitis requires that more attention and thought be given to the sensory side of the reflex arc. In this paper an attempt has been made to show the influence that selective inhibition of sensory stimuli has on the patient's ability to control his muscles. During sleep the adventitious muscular movements cease. The effects of ether, alcohol and sedatives were mentioned. The effects of reducing or concentrating visual stimuli in talking, walking and use of hands were noted. The effect of selective inhibition of sensory stimuli by developing interests in piano, golf, chemistry and bacteriology was pointed out.

In conclusion it may be said that those natural or environmental stimuli which affect the normal individual also affect the cerebral palsy. Indeed it is indisputable that the cerebral cortex receives these stimuli, visual, auditory, proprioceptive sense, etc., summates these stimuli and transfers them to their proper channels for their final release through motor or other pathways. In the cerebral palsies where there is considerable damage to the cerebral cortex and the ideational centers are preserved these stimuli affect the injured brain in a manner shown in the individual cases. A shunting of one or more sensory stimuli will affect the cortex in degrees and thus the final release will be somewhat more towards the normal, as for example, the spastic athetoid cases mentioned who have great difficulty in doing simple acts like feeding themselves and yet are able to do skilled acts satisfactorily like playing golf, playing the piano, and working out laboratory problems in chemistry and bacteriology. With educational training new channels of release will be provided, a partial inhibition of sensory stimuli will be accomplished, and in due time a summation of these sensory stimuli will result in more or less the normal manner.

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THOUGHTS ON HYPERTENSION *

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WHETHER hypertension is a disease or a symptom is a much debated question. It can, I believe, be answered rather easily, for the present at least, in the following way. When we know the cause or the apparent cause we emphasize it and consider the hypertension as part of the symptom complex. When we do not know the cause we look upon the hypertension as the disease itself. On this basis such hypertension as that of chronic nephritis or aortic insufficiency is a symptom, while that of unknown cause is a disease entity. Such a disease entity is represented by essential hypertension.

Although my main object is to deal with essential hypertension, I shall for purposes of clarity give a tentative classification of hypertension. As long as our knowledge of the etiology is limited, such a classification has to be mainly clinical.

CLASSIFICATION OF HYPERTENSION

- 1 Primary, essential or arteriolosclerotic
- 2 Arteriolitic or malignant
- 3 Nephritic
- 4 Secondary or accidental
 - (a) Aortic insufficiency
 - (b) Coarctation of the aorta
 - (c) Adrenal tumors
 - (d) Pituitary basophilism
 - (e) Hyperthyroidism
 - (f) Pregnancy
 - (g) Enlarged prostate
 - (h) Arteriovenous aneurysm

Subclasses

- 1 Juvenile
- 2 Superhypertension

I need say little about this classification—it is largely self-explanatory. With regard to malignant hypertension, I might say that I do not believe it is a late stage of essential hypertension. It is a different disease and has all the earmarks of a distinct clinical entity. In my experience it has occurred earlier in life than essential hypertension. The diastolic pressure is much higher than in the majority of cases of the latter. Renal changes are pronounced. The peripheral vessels are thickened, tortuous, tense and hard.

* Read by invitation before the Academy of Medicine of Northern New Jersey, Newark, New Jersey, May 11, 1937.

Retinal changes are present. The patient looks pale and sallow, his color has been compared to that of a cold buckwheat cake. Cerebral accidents are common.

On account of the necrotic inflammatory changes in the arterioles, the term arteriolitic hypertension is applicable.

The secondary types of hypertension need not detain us, except to say that the hypertension in some of the conditions is compensatory, in others, the connection between cause and effect is obscure.

Juvenile hypertension and superhypertension are entirely arbitrary classifications. By juvenile hypertension I mean a premature hypertension occurring usually from just before puberty to about 35 years. My associate, Dr Stanley E. Harris, has found many instances among students at the University of Pennsylvania and I have seen a number of examples in my office. We admit to this class only those cases in which the blood pressure has been repeatedly tested and found elevated—150 and upwards.

Superhypertension is applied to those cases in which the blood pressure is 260 and higher. I have put them as a separate class so that I can better watch them and note their progress. Such a procedure will eventually be helpful in arriving at a more securely based prognosis. I have had under observation a considerable number of women with systolic pressures of 270 who lived for many years. One, a member of my own family, who for over 30 years had a pressure of from 200 to 275, was nearly 100 years old at death.

Essential or primary hypertension is the most important type, being responsible for 15 per cent of all deaths after the age of 50 years*. It is the principal factor in what I have called *the failing heart of middle life*. The most striking objective result of essential hypertension is enlargement of the heart. At times one finds the heart enlarged in the absence of valvular disease and of concomitant hypertension. In the majority of such cases we may infer that a hypertension existed previously but had disappeared.

I shall not discuss in any detail the theories advanced in explanation of essential hypertension, because I should have to say after each one "not proved." A few points of interest may however be mentioned.

Hypertension is uncommon among the Chinese. Even foreigners living in China tend to have lower blood pressures (Foster¹). Gunewardene² examined 200 Buddhist priests ranging in age from 30 to 80 years and found only one instance of real arterial hypertension. This striking difference between the oriental and the occidental has been attributed to differences in stature, muscular development, climate, habits of diet. But none of these nor all of them combined are sufficient to explain the difference. The greatest difference lies in their respective attitudes toward life. To the Buddhist priest the restlessness, the consuming ambition of the western business man are unknown and incomprehensible. He is never in a hurry,

* Cardiovascular disease, and in this hypertension is the chief factor, causes four times as many deaths as cancer.

never runs, not even as Gunewardene says, if his robes caught on fire His only concern is life after death or some metaphysical problem The placidity of the Chinaman is proverbial

Foster thinks that in the Chinese the widespread use of watermelon seeds which apparently contain a substance that depresses blood pressure may be another factor in the lower vascular tension of the Chinese

Of etiologic factors often not sufficiently appreciated I want to refer to two

1 The possible influence of psychologic disturbances both in causing permanent hypertension and in producing temporary rises above the patient's habitual level Disturbances in the sexual sphere, frustrations, etc., mental strain from business or domestic worries, unsatisfied ambition—seem to be capable of raising the vascular tonus

2 Heredity That heredity is an influential factor in hypertension is easily demonstrated, but that is merely a statistical fact which offers no fundamental explanation We do not know what genes transmit the tendency or where the point of attack is on the blood vessels—on the vasomotor mechanism or on the musculature of the vessels, or back of both, on one or more of the hormone-secreting glands The problems are endless

It seems logical to place the immediate cause of hypertension in the arterioles, in the precapillaries What is the nature of the process in the vessels? The variability, the lability of the blood pressure in essential hypertension, the absence of structural, that is inflammatory or degenerative, changes in the arterioles in hypertensive persons dying in the early stages of their hypertension, suggest that spastic constriction of the arterioles in a large vascular bed such as the splanchnic area is the likely cause For that reason I would make arteriolospastic and essential synonymous words

Having carried essential hypertension back to the arterioles, to arteriolospasm, still leaves unanswered the question, what is the cause of the spasm It is most probably chemical or hormonal in nature It would, however, be an incomplete view of essential hypertension if we considered merely the angiospastic phase The human system is an integration of innumerable quasi-independent mechanisms in harmonious relation, in homeostasis, to use Cannon's word, achieved by the self-steering of all the organs and tissues of body If the neurovascular system shows evidence of disturbance as in hypertension, many fine adjustments are necessary to keep the body functioning At any point in these interdigitating mechanisms a breakdown may occur We are often unable to recognize the early signs of such a breakdown, one reason being that our thinking has hitherto been too anatomic and not enough physiologic It is necessary to study many things At one time the nervous control of the heart was considered the main element in cardiac contraction, until the myogenic theory gained preeminence Perhaps we are at present giving too much prominence to the vasomotor mechanism and not enough to the intrinsic myogenic capacity for contraction and dilatation of the blood vessels

Symptomatology Essential hypertension may be symptomless for many years. It is often accidentally discovered during insurance or health examinations. As long as the heart is competent and able to counteract the resistance in front symptoms are minimal or absent.

The inaugural symptoms are mainly subjective—dizziness, headache, ringing in the ears, palpitation, slight dyspnea on effort, a sense of weight in the chest, nose bleed and irritability. Naturally these need not all be present. There may be only a single one in the beginning. The patient may ignore these symptoms or the unobservant doctor may overlook their cause, contenting himself with purely symptomatic treatment. Such patients eventually come under observation for more pronounced symptoms. These are most variable but are principally cardiac, cerebral or gastric.

The cardiac manifestations are those of early congestive failure—subjectively, dyspnea, objectively, peripheral edema, basal pulmonary congestion or unilateral hydrothorax. These, especially the latter two, must be looked for, otherwise they will be overlooked.

A rarer symptom, which might be called cardiopulmonary, is acute pulmonary edema, which has a tendency to recur at intervals and usually comes on at night. Air hunger, a sense of suffocation and fear of impending death, together with intense cyanosis, the physical signs of pulmonary edema, and at times but not constantly the expectoration of blood-tinged frothy fluid are the characteristic symptoms.

An attack of angina pectoris or of coronary occlusion may be either an early or a late symptom.

If the patient presenting such symptoms is carefully examined one or more of the following conditions will be found:

- 1 A high systolic and a relatively low diastolic pressure
- 2 Cardiac enlargement
- 3 Accentuated second aortic sound
- 4 Often a systolic murmur at the aortic area
- 5 In late stages a systolic murmur at the apex
- 6 The radial vessels are usually soft but the temporal arteries are often tortuous
- 7 Arcus senilis or annulus senilis
- 8 There may be basal râles
- 9 Hydrothorax, generally unilateral
- 10 Edema of the shins and ankles
- 11 Changes in the retinal vessels

The electrocardiograph may show left axis deviation, in cases of long standing hypertension the degree of axis deviation may be marked, with prolongation of the QRS interval beyond the accepted top normal figure (0.1 second) due to increased conduction time through an hypertrophied ventricle. T_3 may be inverted and, according to Master, T_1 may also be inverted.

Many clinicians in speaking of the enlarged heart of hypertension use the term myocarditis. Strictly speaking this is not correct, for only rarely is there any evidence of inflammatory changes. Nevertheless, the heart muscle gives out. In order to get rid of the inappropriate term myocarditis, I have proposed myocardosis as a generic term to imply a functional rather than a structural change.

Cerebral Symptoms These are extremely interesting and important for the understanding of the morbid physiology of hypertension. As a rule the disturbances are transient—hemiplegia, aphasia, monoplegia—and are usually ascribed to local angiospastic states. In severe cases generalized convulsions may occur which are often wrongly called uremic or epileptic. There may be no evidence of kidney damage and, setting in late in life, after fifty, they are not true epilepsy. Some speak of the condition as hypertensive encephalopathy, it is also called epilepsia tarda.³

During the convulsive seizure, and also in other types of encephalopathy before the onset of the particular symptom there is usually a sudden and abrupt rise in the systolic blood pressure, at times to 280 or even 300.

The focal symptoms mentioned above may last from a few minutes to 24 or 36 hours and may then subside without any residue. However, I have observed in numerous instances the persistence of one particular symptom, namely conjunctival anesthesia on the side that had been affected. I found this even in cases in which there was no anesthesia of the general body surface.

Besides angiospastic complications hypertension may lead to thrombosis and to rupture of cerebral vessels, i.e., to apoplexy, which is a frequent but by no means the most frequent mode of death in essential hypertension.

The gastric symptoms of hypertension are the gastric symptoms of the myocardial weakness, of the myocardosis, associated with and usually secondary to the hypertension. In the majority of instances the chief complaint is fullness and gaseous distention. Such a complaint by a person past 50 years who previously was free of digestive disturbances, is never to be treated lightly—it may mean the beginning of malignant disease or the failing heart of longstanding high blood pressure.

Diagnosis It is important to make the diagnosis of essential hypertension in the early stages for the treatment will then be of most avail. A systolic blood pressure of 140 to 150 in an individual under 40 years is not to be ignored. Naturally it must be checked by several readings on different days so as to eliminate the factor of fear or excitement. A labile blood pressure showing wide swings from high to low is common in persons who later show a permanently elevated blood pressure.

The family history may be of significance. A history of hypertension, apoplexy, chronic heart or renal disease constitutes a background for hypertension in the descendants.

What shall be our criteria for the diagnosis of essential hypertension? As I view the subject these criteria are

- 1 A persistently high systolic pressure
- 2 A relatively low diastolic pressure
- 3 Absence of disturbance of renal function
- 4 Normal blood chemistry, that is as regards urea nitrogen and chlorides
- 5 Absent or minimal eye changes
- 6 A symptomatology trivial compared with the height of the systolic pressure

At this point I might say something about prognosis, since due attention to that rather neglected phase of medical practice may help us in dealing with our patients. I shall be somewhat dogmatic as unconditional statements are more useful, provided they are favorable, in quieting the patient's mind.

- 1 An individual can live to be 80 or even 100 years with high systolic blood pressure
- 2 Women bear high blood pressure better than men
- 3 The diastolic blood pressure is more important as a prognostic index than the systolic blood pressure. A low diastolic blood pressure favors relative longevity
- 4 Good renal function—traces only of albumin or no albumin, a few hyaline casts, good concentration—is a favorable prognostic finding
- 5 Moderate cardiac hypertrophy is not unfavorable
- 6 Cerebral accidents even of apparently trivial nature as well as anginal pain and retinal hemorrhages are all ominous signs

Treatment The treatment of essential hypertension is psychologic. By that I mean that it must be addressed to the intelligence rather than to the stomach of the patient. Such treatment ought to be part of our general scheme of preventive medicine in the sense that we should know the vascular characteristics, the tubing as Osler called it, of our patients and of their children. It certainly would give us valuable information if we were to examine the children of a man or woman in whom we had discovered high blood pressure—we might be able so to shape the lives of these persons as to guard them against hypertension in later life. To do all this means addressing ourselves to the minds of our patients and making them understand our aims.

We must assure our patients with essential hypertension of the comparative harmlessness of high blood pressure. To some extent we physicians have been responsible for making the laity blood-pressure-minded. A goodly number of patients have come to me all in a tremble saying, "Doctor, I've got blood pressure." When we can conscientiously do so we must relieve such persons of their anxiety.

Is it wise to tell the patient who has hypertension what his blood pressure is? Here the psychologic insight of the doctor and the general circumstances of the case must be the guide. My rule is this. If the patient is cooperative, then there is no need of his knowing his top figures. If he

is uncooperative, then it may do good to tell him so as to scare him into good behavior

Many hypertensive patients overwork, overeat, undersleep, and over-smoke. All these departures from the norm must be corrected. The man who takes to bed with him "the cares that infest the day" must be educated in a better habit. Attention must be given to the sexual life in both sexes—not that we can often help, but we can better understand. In some cases we can actually help—by advising infrequency of coitus when dealing with patients with superhypertension or with those approaching it.

Diet Dietetics is the weakest subject in medicine. One can find authority for almost any conceivable diet for any human ailment. At one time it was customary in hypertension to give a salt-free, low-protein diet. However, excepting in those who indulge in meat and salt to excess, such extreme restriction was of no particular value in reducing blood pressure. All it did was to make the patient's life miserable. Moreover, Vilhjalmur Stefansson has shown that one might subsist on an exclusive meat diet for a year without any elevation of the blood pressure. Yet that might not apply to one who by heredity was destined to have high blood pressure, for such a one a low protein diet may be wise.

I think physicians are generally agreed that quantity is more important than quality, especially if the patient is overweight as is so commonly the case. We serve our patients best by teaching them moderation.

Alcohol has been under suspicion but in my opinion unjustly. It is true many free drinkers are hypertensive but such men as a rule are also free livers. A little whisky or a social glass of wine does no harm to the blood pressure.

With respect to tobacco, my opinion is quite different. I usually advise a minimal amount of smoking and if the patient has had cardiac pain I as a rule forbid tobacco altogether.

The bowels need attention. The patient should have a regular, easy, daily movement or two movements without straining. If need be, he should take a laxative, such as mineral oil or compound licorice powder. Toxic symptoms—occipital headache and mental depression—are sometimes quickly relieved by a colonic irrigation but this is not needed with any great frequency.

I have found in particularly constipated people that a weekly dose of castor oil is helpful.

Exposure to the hot sun should be avoided.

Exercise within reasonable limits is permissible. The trouble is to find the "reasonable limit." Wading in a swift stream to catch trout or salmon involves not only a severe physical but also an intense emotional strain—more than is good for a hypertensive fisherman. A prolonged golf game in the hot sun is likewise fraught with risk. Then there are persons, usually bankers or captains of industry, who are given to violent home gymnastics.

—their habits must be studied and modified to suit their cardiovascular condition

Medicinal Treatment There is no specific drug in our pharmacopeia that will permanently lower arterial blood pressure. Many have been recommended, all have been found wanting. Their very number is proof of what I have said. I have used bismuth subnitrate, potassium sulphocyanate, and various organic extracts. They have all proved unreliable. Does that mean we are powerless in dealing with hypertension? By no means. The best results are obtained with sedatives, particularly those of the barbituric acid group. Phenobarbital in one form or another is very useful. The bromides are also helpful. One can combine them with advantage with elixir phenobarbital. I also like chloral hydrate which in reasonable doses is perfectly safe.

When the pressure is high and the heart begins to labor or convulsions occur or acute pulmonary edema, venesection often brings about immediate and dramatic relief.

In women at the menopause it is perhaps rational to try some of the endocrine products. If one takes the words of detail men or of the pharmaceutical literature as gospel, then these are sovereign remedies. We need to know a great deal more about them before any such statements can be made.

When the pressure is abnormally high, one may give the nitrites. I prefer for regular use erythrol tetranitrate in doses of 0.015–0.03 ($\frac{1}{4}$ to $\frac{1}{2}$ grain). In any emergency and when the patient has cardiac pain nitroglycerin under the tongue is the best remedy.

Roentgen-ray therapy has been used on the adrenals and on the pituitary gland, the latter on the theory that pituitary basophilism might be the cause of essential hypertension. The data are as yet insufficient for a definitive conclusion.

Physiotherapy, including diathermy, has been tried—personally, I have not seen much benefit from these measures.

Surgical Treatment The general futility of medical treatment in established hypertension made the search for a surgical method altogether natural. A number of our boldest surgeons have devised procedures consisting in the main of cutting off the vasomotor supply to the abdominal arteries and arterioles. Theoretically this seems rational and can be attempted in various ways. It is not my present purpose to go into the history of this subject. Suffice it to say that the principal contributions are from the Mayo Clinic, from Adson and his coworkers, from the Crile Clinic, from Ann Arbor by Peet and his associates, and from the New York Hospital by Heuer and Page. One of the first attempts made to treat essential hypertension surgically was that of George Crile, who about 1910 performed a unilateral adrenalectomy. The operation was followed by a temporary fall in the blood pressure which later rose again to the preoperative level. This temporary success led Dr. Crile to add to the unilateral adrenalectomy

partial resection of the other gland. The blood pressure was affected somewhat more than by the unilateral adrenalectomy alone but it rose again to the disease level.

Crile next attempted to attack the function of the adrenal glands which he held responsible for the hypertension, by denervating the glands in two stages. This had a better effect, the improvement or cure lasting in some cases as long as five years. But recurrences were still common. He therefore extended the operation to include resection of the larger, minor and least splanchnic nerves, but even then results were not what had been expected, so that another approach was chosen, namely resection of the celiac ganglion and denervation of the aorta. The results in 25 instances, chiefly cases of malignant hypertension, have been most encouraging. The operation can be performed under nitrous-oxide-oxygen anesthesia.

Adson and his colleagues at the Mayo Clinic have employed two operative procedures.

- 1 Extensive bilateral section of the ventral roots of the lower thoracic and upper lumbar nerves.

- 2 Extensive subdiaphragmatic sympathectomy, which includes the splanchnic nerves on each side as well as the two upper lumbar ganglia and biopsy or partial resection of the suprarenal gland. It is still too soon to draw definitive conclusions as to the value of these operations but from observations to date Adson, Craig and Brown⁴ prefer the subdiaphragmatic splanchnic resection with removal of the upper two lumbar ganglia and resection of the suprarenal gland.

Page and Heuer⁵ in 17 patients performed section of the anterior nerve roots. They conclude that although the operation has markedly improved the clinical condition of many of the patients studied for periods up to 2½ years its ultimate value in the treatment of hypertension has not been established. In their most recent article⁶ they offer no encouragement.

From reading reports about surgical operations for the cure of hypertension and from my own very limited experience and from reports given to me by my surgical colleagues at the University Hospital, I would conclude that surgery as at present practiced has a long way to go before it justifies itself. But this does not preclude the possibility that some surgical method may be found that can be looked upon as curative. Perhaps we shall go through a stage similar to what occurred in the surgical treatment of hyperthyroidism. There was much criticism of the early operations. But that criticism has vanished before improved technique at operation and better pre- and postoperative care.

The pharmacologist, the biochemist, the clinician, must also continue their intensive studies in the hope of finding the chemical agent that causes vascular spasm. Perhaps the Banting of hypertension has been born.

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THE RELATION OF EMOTIONAL STRAIN TO ILLNESS ¹

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EMOTIONAL strain is an expression which is not readily described by words but is better appreciated by reference to personal experience and probably requires a measure of introspection for its understanding. However, emotional strain seems to be the best expression to describe the condition resulting from social or personal maladjustments which produce annoyance, tension or minor emotional disturbances over prolonged periods. Thackeray says in effect in "Vanity Fair" that it is not the great sorrows, but the little troubles that one daily has to bear that make life hard. It is the troubles that patients have to bear daily that cause emotional strain. It is often related to illness and becomes so closely integrated with it that emotional strain and illness are often inseparable and constitute two phases of a single problem, neither of which can be dealt with effectively alone.

For an appreciation and evaluation of emotional strain, consideration must be given to the personality and physical condition of the patient, the ideas, sensations and symptoms which he can express and describe, and the conditions of his environment, including his social status. Emotional strain is determined by the causes of emotions, the type of person in whom they are aroused and the character of the emotional reactions. This simple formulation is indeed superficial and does not bring into consideration psychopathological states or deep-seated psychic disturbances requiring even "minor" psychoanalysis for their disclosure. It is intended as a formula for the routine use of the practitioner of medicine, in order to reveal and evaluate the emotional components of almost every illness which brings the patient and doctor together.

It is well known by every intelligent person today, layman as well as physician, that many ailments are caused or modified by emotional strain, and many forms of treatment by various sorts of healers are successfully practiced on the basis of this knowledge. Although the private practice of medicine concerns itself, of necessity, with the emotional disturbances of patients, the organization and routine of the general hospital as operated today does not provide a large place for the study of the total individual and of the situations productive of psychogenic symptoms. Nor has it been practical to combine with the thorough and somewhat specialized form of medical education studies that lead to an understanding of the relation of

* Received for publication June 10, 1937

From the Department of Medicine of The Johns Hopkins University and Hospital
This paper is from a study supported by a grant from the Rockefeller Foundation

personal and social problems of patients to their illness, except in psychiatric teaching

Because of the foregoing considerations, an investigation of the nature and extent of emotional strain as related to illness has been undertaken in the Johns Hopkins Hospital, and measures for its relief, combined with the therapeutic regime prescribed for patients, have been employed. The study has been carried on with almost no attempt to select "suitable" cases, except that most of the patients have been those admitted to the wards and to the general dispensary of the medical service. Of the first 173 patients studied, in 83 or about half, emotional strain was found to form some part of the total clinical picture. In most of these patients organic disease existed and in some of them emotional strain played but a minor part, while in others it was the major factor in understanding the full meaning of the illness and in the treatment of the patient. This study has demonstrated clearly that emotional strain is of more importance as a component of illness in the usual run of hospital patients than had been suspected. The study was undertaken with the conviction that it would reveal certain so-called "accessory factors of health" which were not being considered as fully as might be desirable for the complete medical care of patients, even in a hospital where an unusually high standard of medicine is practiced and where there is a pervading interest in the patient as an individual.

The approach to the patients has been that of a clinician, and the study, diagnoses and treatment by the members of the hospital staff have first been carefully reviewed in order to have a clear conception of the physical status of the patients before the first interview. Patients have then been seen either on the wards or in the office adjoining the dispensary, and their personal and social histories have been expanded and their symptoms further analyzed in the light of the physical findings and laboratory studies.

Whenever any evidence of emotional strain has been revealed, the patients have been further studied in various ways, by home visits, interviews with other members of the family, the study of hospital records of other members of the family when they exist, inspection of working conditions, reports from social agencies and information from various other sources. In this work Miss Josephine C. Barbour, an experienced medical social worker, has been a valuable collaborator. This study is to be reported in detail subsequently.

It is the purpose of this paper to report a single case as an example of emotional strain as related to organic illness, to describe the method of its study and to discuss its significance in relation to treatment. The case is an illustration of how a rather simple social maladjustment may be relieved by a procedure requiring no special technical training and by the application of nothing more than the use of common sense after the cause of emotional strain is revealed.

CASE REPORT

The patient, a 56-year-old white woman laundry worker, was referred to the general medical dispensary from Ophthalmology where she was under treatment for immature cataracts and an error of refraction. She was admitted on January 7, 1936 to the medical dispensary, where she has been studied and followed by Dr. A. Murray Fisher. She complained of poor vision and hoarseness. Her history at this time contained almost no other symptoms. She had lost three or four pounds in weight recently. The hoarseness had been present for nine years, and she attributed it to the atmosphere of the laundry. The history states that she had no headaches, dyspnea, precordial pain or swelling of her ankles, but had nocturia two or three times nightly. She said she did not feel nervous, but on a subsequent visit she said her work was quite hard and that she becomes excited and very nervous at times. She had had an attack of "pleurisy" 11 years previously, but had otherwise had good health.

On physical examination the patient was found to be a fairly well nourished blond woman weighing 118½ lbs., with a flushed face and a rather loud, husky voice who appeared somewhat restless and emotional, with moist skin and a rather coarse tremor of the hands but no exophthalmos. The thyroid gland was palpable but not definitely enlarged or nodular. There was marked pulsation in the episternal notch, and the veins of the neck were engorged. Lungs were clear. Substernal dullness was somewhat widened but there was no cardiac enlargement. A systolic murmur in the aortic area and accentuation of the second aortic sound were noted, with a heart rate of 96. The systolic blood pressure was 210 and the diastolic 120 mm. Hg. The physical examination was otherwise negative. The Wassermann reaction was negative. The basal metabolic rate was plus 23 and a teleroentgenogram showed the heart shadows to be within normal limits, with moderate tortuosity of the aorta. There was a faint trace of albumin in the urine. The phenolsulphonephthalein excretion was 52 per cent in two hours and her hemoglobin was 92 per cent.

The basal metabolic rate was repeated twice at weekly intervals and determined as plus 29 and plus 45, the systolic blood pressure being 235 and the diastolic pressure 130 mm. Hg at the time of the first of these estimates, and 230 and 130 mm. Hg respectively at the time of the second.

A diagnosis of arteriosclerosis with arterial hypertension was made. The evident emotional tension, venous engorgement, marked hypertension and elevated basal metabolic rate led to the conclusion that the patient was threatened with cardiac failure, and a change of occupation and more rest were advised.

The patient was interviewed on February 27 and subsequently a visit to her home was made, the interview being undertaken as a routine measure in a process of sampling dispensary cases without selection because of any apparent problem. She was found to be an employee of the laundry of the Johns Hopkins Hospital where she had worked for nine years. During the past four years she had been quite nervous and emotionally disturbed, somewhat excited and had felt almost constantly "uncomfortable" while at work. Recently she had felt the strain of her work especially, and it now disturbed her so that she became excited and very nervous. During the past three months she had had shortness of breath on exertion especially noticeable on walking up a moderate grade to her work, so that she had been obliged to go to work slowly and by a longer route which avoided the grade. She slept well, but was quite "unhappy" and had a sense of dread on going to work. She had no muscular fatigue, although she stood constantly while at work.

The personal history and social status of this patient indicated that she had experienced severe emotional disturbances in her past life especially connected with her marital history. She had a satisfactory childhood as a member of a large family of seven children who were apparently quite congenial. Married at 21, her first husband was killed in a street accident about a year later, leaving her with an infant,

now a man of 34. She married again two years later, and soon began having difficulties, as her husband proved very unreliable and supported her for a number of years only on court order, leaving her and returning frequently, "as often as fifty times," she thinks. During this marriage two sons were born, now 31 and 28 years old. She was legally divorced seven years after this marriage, and five years later she contracted a third marriage which was also unsuccessful, ending in divorce without issue after about four years. The patient was 40 years old at this time, and at the age of 46 she began to work in the laundry of the Johns Hopkins Hospital, where she has been employed constantly for the past nine years.

The patient lives with one of her married sisters in a comfortable house of which she occupies the third floor. Her sister has been having "heart attacks" for a number of months, and suffers from shortness of breath and swelling of her ankles at times. Her brother-in-law is a pipe-fitter by trade, but has had no regular work for five years, and recently has been employed as a laborer on a WPA project. He owns the house in which they live, but has been unable to pay his taxes for two years. The patient's three sons are unable to help her financially, as one has only part-time work, one is without a job while his wife works, and the third earns but little selling on commission. The patient is therefore entirely dependent on her own earnings.

The patient said that her work in the laundry went well until four years ago when she was promoted to be in charge of the flat ironing machines, with four girl helpers. The patient is unusually conscientious and tries hard to keep the work speeded-up, but is much annoyed by the young women who help her, as they are inattentive and "loaf on the job" when the forewoman is not in sight. The work has increased in volume in recent years, and she does not like it because of the "nervous strain." She said she noticed a complete change in her feelings when she was on a vacation during the summer of 1935, during which time she felt quite well.

From this history it was inferred that the vascular hypertension of the patient was probably related to the various emotional episodes of her married life, which had, we believe, made her especially susceptible to emotional strain. The severity of her hypertension indicated that she should be relieved of emotional strain as far as possible, and it was evident that tension and emotional disturbances were related to the conditions of her work.

In order to observe the patient's working conditions the assistant director of the hospital in charge of personnel was consulted, and a visit with him was made to the laundry. The patient was seen with her helpers, girls of 18 or 20 years who apparently had no particular interest in their work, which consisted in shaking out laundered clothes and placing them on the flat ironing machines. The work had to be kept up to a certain speed, in order to coordinate it with the other processes in the laundry, and the patient seemed to take the full responsibility for this. The superintendent of the laundry said that the patient had recently been failing in her work, as she did not have the necessary authority over her assistants, who teased and laughed at her. He said a change in her work would be helpful to the work of the laundry as well as to the patient. The superintendent agreed to change the work of the patient so that she no longer had the responsibility for other workers, although this could be done only with a reduction of wages of about \$1.50 a week in fairness to other workers. The plan was then explained to the patient, the change being suggested as necessary for her health. After some hesitation and with some sense of disappointment, the patient agreed and her work was changed to sorting clothes on the other side of the flatwork ironing machines. This change was made on March 12, 1936.

The patient was seen on March 19, one week later, and said with enthusiasm that "a miracle has happened, and a big burden has been lifted from me." The feeling of excitement had gone, her neck, she said, no longer swelled and she was no

longer nervous or short of breath Phenobarbital, prescribed one month previously, was discontinued by Dr. Fisher.

The patient has now been followed for over a year since her work adjustment and she has had no return of her previous symptoms. She continues to speak of the effects of the change as "a miracle" and has continued to work steadily, taking no drugs and no longer avoiding the up-grade walk to her work, as it now causes no shortness of breath. She has gained in weight up to 135 lbs. and gives the impression of being a contented, happy person. She no longer appears excited, her voice is not "husky," the face is not flushed and the neck veins are not engorged. Her basal metabolic rate was estimated at plus 20 in May, and plus 4 in December 1936.

The patient has been seen at monthly intervals or oftener, since January 1936 to May 24, 1937, and her blood pressure has been measured sitting up, lying down and after rest, with the object of finding its lowest level.

The blood pressure has shown no appreciable change throughout the period of observation, its lowest level having been 210 systolic and 120 diastolic, while on April 30, 1937 the systolic blood pressure was 245 and the diastolic 135 mm Hg.

The point of special interest in this case is the almost sudden disappearance of her symptoms when she was relieved of an emotional strain, without any change in her elevated blood pressure. It was natural to attribute her symptoms as primarily caused by the somatic or organic disease from which she suffers, and the adjustment of the conditions of her work was undertaken with the idea that it might have a beneficial effect on her blood pressure. The effects of the work adjustment were, however, different from what was expected, but are instructive, as well as of much value to the patient.

There was a social maladjustment between the patient and the workers she was expected to control and direct. Her own conscientious spirit was in conflict with her young and inattentive assistants, and she did not have sufficient leadership to impose her authority upon them. As this situation had existed for four years with increasing lack of success and with changing assistants, the patient had been under a long emotional strain which had evidently been the main factor in the production of her symptoms. Mayo,¹ in his study of the human problems of an industrial civilization, shows the striking relation of proper social adjustment to the output of industrial workers, and our case suggests that the social adjustment of workers may have a definite relation also to their state of health.

It is interesting to note that among the changes which the patient reports is her ability to walk up the grade on her way to work without dyspnea, while for three months previous to her change of work, she felt forced by her dyspnea to avoid this grade. She also stated that she previously had a feeling of dread on going to work, which has disappeared. These statements are suggestive that the dyspnea was of psychogenic origin, and calls attention to the value of looking for psychic influences in the production of symptoms, even when there may seem to be a satisfactory explanation for them in the existing organic disease.

The change in the basal metabolic rate is also of interest, it having been as high as plus 45 in January 1936, and having been estimated as plus 4 in

December of the same year. The fall in the basal metabolic rate may have resulted from the ability of the patient to attain a more nearly basal state with the disappearance of excitement, or it may have had some other cause.

The relation of an elevated basal metabolic rate to emotion is familiar to all who have worked in this field, but its significance is not clear, although a number of investigations of this subject have been published.

Dunbar² has reviewed a number of these studies and says that the literature is inconclusive because the basal metabolic rate has not been usually correlated with the emotional state of patients but with certain disease groups. Landis³ has studied the effect of emotions on the basal metabolic rate, and finds that an unpleasant emotion, produced by suggestion, is usually attended by a rise in the metabolic rate, and considers this rise as resulting from (a) increased supra-renal or thyroid (?) activity, or (b) increased metabolism of the central nervous system, or (c) increased muscular tonus and incomplete relation. His own experiments are not consistent, as changes in the basal metabolic rate were not always in the same direction or of the same magnitude with the same degree and kind of emotional disturbance. He concludes that changes in metabolic rate cannot be considered as a direct measure of emotional disturbances or cumulative emotional upset. DuBois⁴ discusses the influence of emotion in elevating the basal metabolic rate, and gives some examples to illustrate it, but he offers no further explanation of the phenomenon.

It is evident that our present state of knowledge does not allow a definite interpretation of the change in the metabolic rate that occurred in our patient, but it is of interest to note that there was a well defined decline to a normal level from a distinct elevation with the disappearance of the subjective symptoms after the removal of emotional strain.

This patient is one of many in whom social and personal problems have been found to produce emotional disturbances leading to symptoms, either associated with or without outspoken organic lesions. This patient presented an unusually simple problem which was relatively easy to study and to solve, followed by such striking changes in symptoms as to leave no reasonable doubt as to the relation of cause and effect. The fact that the changes in symptoms occurred without any observable alteration in the outspoken vascular hypertension, indicates the value of studying patients with seemingly unalterable pathological conditions, from the point of view of emotional disturbances. They may be the major cause of distress and disability, and deserve the same careful attention that is given to the organic disease.

It is the daily experience of every practitioner of medicine to see patients whose symptoms are not adequately explained by the findings of the physical examination and laboratory study, especially if a rigid analysis of symptoms in relation to objective findings is made. When a patient presents definite evidence of disease the objective findings outweigh the symptoms of the

patient as the basis for diagnosis and treatment. Attention is focused on symptoms, however, when the objective findings reveal little evidence of disease or when they cannot be related to the complaints of the patient. Then the symptoms are usually recognized as of psychogenic origin. The tedious task of attempting to determine the psychogenic or emotional factors responsible for the symptoms is not usually fully carried out in hospital practice unless they seem of sufficient seriousness to call for a psychiatric consultation, or to lead to the transfer of the patient to the psychiatric service. In many hospitals these desirable procedures are impractical, even for patients with well-pronounced emotional disturbances, and in many cases, patients with symptoms of psychogenic origin are discharged from the wards with encouragement and reassurance, to be followed in the out-patient department or if already there, they are given sedatives, advice and at times referred to the medical social worker. These procedures are often beneficial, but too often the benefits are transient when the underlying causes of emotional strain remain uncovered and unconsidered in the plan of treatment, and patients continue to search for health by many visits to the dispensaries and by various types of special examinations and treatments.

The extent to which harmful emotions may be related to illness is strikingly shown by the extensive literature on the subject that has been collected and reviewed by Dunbar² in her book on "Emotions and Bodily Changes," in which it is indicated that emotional disturbances may affect practically every organ in the body and may play a part in many diseases. Cannon,⁸ whose study of the physiological effects of emotions has continued throughout his many years of research, has recently expressed the opinion that the medical profession has not recognized in a practical way the nervous strain of modern life as a cause of disease, and he emphasizes the importance of regarding man as a "mind-body" unity. He discusses the ways in which success may be achieved in the treatment of emotional disorders by efforts to affect the emotions so that they are no longer harmful in the physiological sense, and will therefore cease to produce "tensions" and turmoil, responsible for many symptoms of illness causing distress and disability.

The study of the emotional components of illness presents many difficulties when an attempt is made to apply to patients the knowledge which the physiologists have developed, but in spite of this, it is the task of the physician to endeavor constantly to gain a better understanding of the effects of emotions in terms of established scientific facts. The case reported in this paper is offered as an example of how causes of emotional strain may be uncovered and removed without perhaps revealing the true, basic nature of its harmful action. Greater insight into these problems will come, however, as practitioners in various fields of medicine come closer in their attitudes and work with the psychiatrists, and when psychiatrists have more opportunity to study the emotional disturbances related to organic disease.

Meyer has for many years emphasized the psychobiological point of view as a field of science which should pervade medicine in all its phases, so that an understanding of the psychic aspects of illness may be progressively developed with the increase of experience and skill of the medical practitioner in any special field he may choose to cultivate. In speaking of the recognition and treatment of visceral and somatic symptoms which spring from mental causes, Meyer¹ says, "These disorders are common enough to make it a responsibility of any physician to learn something about the mental causes and their working. It is not likely that the general practitioner and the internist will be able to do their best without such knowledge. It will have to be acquired by a study of these events when and where they occur, with attention to the situation and to the facts that make reactions excessive."

It is surely true that emotional disturbances must be studied when and where they occur, and it cannot be foretold when or where they are to be encountered. For this reason constant watchfulness is needed by medical practitioners in every field, if emotional strain is to be given its proper evaluation in the production of the subjective evidence of illness, and in medical treatment. This attitude is difficult to maintain, in the wards and outpatient services of the modern hospital. This circumstance does not, however, diminish the importance of emotional strain in relation to illness, but should stimulate further efforts and new methods.

One of the foremost exponents of the study of the patient as an individual, among the internists in this country, who has given much thought and experimentation to the treatment of illness caused by emotional disturbances, is Dr. Joseph H. Pratt. It is hoped that what is written here may in some way be helpful to the cause in which he is much interested. As this paper is to be included in a volume dedicated to him as a *Festschrift*, it is especially gratifying to recall his encouragement and advice regarding the work of which this paper is a part.

SUMMARY

A study of hospital patients with special reference to their social and personal problems has demonstrated that emotional strain frequently causes an important component of illness, deserving consideration in diagnosis and treatment.

A patient with an apparently unalterable organic disease is reported whose symptoms disappeared with the relief of emotional strain.

The significance of this case as an example of psychogenic symptoms in organic disease and the methods of study and treatment used are discussed.

The need of greater consideration of the patient as a total individual, in order to gain a better understanding of emotional disturbances as related to illness in hospital practice is emphasized.

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THE LIPID AND CHOLESTEROL CONTENT OF THE BLOOD OF PATIENTS WITH ANGINA PECTORIS AND ARTERIOSCLEROSIS

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THE present study of the blood cholesterol and lipids in patients with angina pectoris of arteriosclerotic origin was prompted by the general interest in the relationship of cholesterol metabolism to the pathogenesis of arteriosclerosis. No systematic study of the cholesterol and lipid constituents of the blood in patients with coronary sclerosis is available in the literature.

There are, however, some studies on the cholesterol concentration in the blood of patients with arteriosclerosis. Bachmeister and Henes,¹ in 1913, after a study of 13 patients with arteriosclerosis and of nine normal individuals, stated that patients with atherosclerosis in the stage of development showed an increase in the blood cholesterol, but that no deviation from the normal was found when the process was stationary. The evidence presented was inconclusive. Weltmann,² without giving details, also reported increased values in 11 out of 12 patients with arteriosclerosis complicated by other diseases. It was his impression that hypercholesterolemia ran parallel, to a certain degree, with the severity of the arteriosclerosis. Denis,³ in 1917, unconvinced because of the number and variety of conditions in which abnormal cholesterol values were reported, studied the cholesterol in 14 patients with atherosclerosis and compared their values with those of 20 normal individuals. The values of the normals varied from 167 mg to 225 mg per cent, and were essentially in agreement with Bloor's normal figures⁴ for the same method. Five of the 14 patients with arteriosclerosis showed values of 250 mg or above, these five patients had cardiac disease or nephritis. One of these had angina pectoris and a cholesterol value of 268 mg. Gorham and Meyers⁵ also studied 10 patients with atherosclerosis and compared their values with those of 14 normal individuals. The values of the atherosclerotic group varied from 160 to 230 mg, those of the 14 controls, from 130 to 190 mg per cent.

In the reports mentioned, no careful consideration was given to the criteria employed in the selection of patients with arteriosclerosis. Mjasnikow⁶ in 1926, presented more convincing evidence that he was dealing with arteriosclerosis. He used the following criteria: orthodiagraphic evi-

* Received for publication April 9, 1937

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dence of enlargement of aorta in the absence of syphilis and hypertension, aortic murmurs, and clinical symptoms of coronary disease. He employed two colorimetric procedures^{7,8} and finding a constant difference between them recorded his values with one, the method of Grigaut. In 16 patients with arteriosclerosis, the blood cholesterol was elevated in every instance, 12 of these patients had angina pectoris. For control data he relied on the normal values for the method used and the results in his non-arteriosclerotic patients. These normal values varied from 120 to 170 mg, those in the arteriosclerotic group, from 190 to 440 mg. In a second group of 25 patients in whom the diagnosis of arteriosclerosis was less certain, there were elevated values in 10 instances. Koulikov, Veiland and Tarnopolskaja⁹ in 1931, studied cholesterol values in patients with cerebral arteriosclerosis, and noted increases in some instances. Their data, however, are too incomplete to permit proper evaluation.

Stepp¹⁰ on the other hand, without offering evidence, stated that he was unable to find any abnormality of the blood cholesterol in patients with arteriosclerosis. Andes, Kampmeier, and Adams¹¹ came to a similar conclusion, these latter authors studied the blood cholesterol in 35 healthy medical students and compared values with those of 31 negroes, 16 of whom showed atherosclerosis. Of these 16, the ages in 11 varied from 20 to 30 years, and vascular disease was judged by compression of brachials, and in some instances, the condition of the dorsalis pedis. Elliot and Nuzum¹² in a study of the cholesterol values in hypertension incidentally estimated the degree of arteriosclerosis in their patients, by considering the condition of peripheral arteries, fluoroscopy of the aorta, and ophthalmoscopic examination of the fundi. In 19 patients with moderate or advanced arteriosclerosis, the blood cholesterol was essentially the same as in their controls.

In 1935, Duff¹³ summed up the published data on the subject as follows: "It is sometimes stated that hypercholesterolemia is regularly associated with arteriosclerosis in man, but such statements are based on a literature much of which has no direct bearing on the question. Some publications which are frequently referred to in this connection have nothing to do with arteriosclerosis as such, but are concerned with various other diseases in which hypercholesterolemia is known to occur and with which arteriosclerosis may be associated. Whatever may be the truth of the matter, it is obvious that these data prove absolutely nothing regarding the occurrence of hypercholesterolemia in association with anatomic lesions of the arteries."

Recently, Lande and Sperry,²⁹ aware of the difficulty in recognizing arteriosclerosis clinically, attacked the problem by studying the blood lipids shortly after sudden death. The total cholesterol was then compared with the lipid content and the degree of gross atherosclerosis of the aorta. No correlation between the level of blood cholesterol and the degree of atherosclerosis was found. Many abnormal values due apparently to such factors as (1) infection during the few hours following the accident and (2) he-

molysis, were excluded, and reliance was placed on the constancy of the ratio of free to total cholesterol as a guide to the accuracy of values obtained. In a study of this kind, however, there are two possible sources of error that would not necessarily alter the free to total cholesterol ratio: (1) dilution of blood serum following hemorrhage (death in most instances followed automobile accidents), and (2) concentration of blood serum attending shock with loss of body fluids. Further, the range, 82 to 446 mg per 100 c.c., of values obtained on these bloods drawn shortly after sudden death was greater than the distribution usually accepted as normal.

In the present study, attention was directed to the following considerations: (1) methods of analysis, (2) selection of patients with angina pectoris, (3) selection of control subjects, (4) statistical treatment of data.

Methods There have been several recent criticisms of the colorimetric methods for the determination of blood cholesterol^{14,15}. For this reason the gravimetric method of Man and Peters¹⁶ in addition to the colorimetric method of Meyers and Wardell¹⁷ with apparatus for continuous extraction described by Ling¹⁸ were used in this investigation. The values obtained by both cholesterol methods on the same blood were compared in 50 instances¹⁹. In general a fairly close agreement was noted. The average deviation of the colorimetric determinations from the gravimetric was plus or minus 8 per cent. Free cholesterol was precipitated with digitonin from the alcohol ether extract before saponification. The precipitates were weighed on a micro balance. Fatty acids and phospholipids were determined by the methods of Stoddard and Drury, and Fiske and Subbarow respectively, as modified by Man and Gildea²⁰. The fatty acids were determined as milli-equivalents and translated into milligrams by multiplying by 277, the average molecular weight of the fatty acids as they usually occur in blood. Measurements were made in duplicate. Venous blood was drawn with minimum stasis from patients in the post-absorptive state. The basal metabolic rate was determined in duplicate with the Collins, Benedict-Roth apparatus and results calculated according to the Aub-DuBois²¹ standards.

Selection of Subjects A large group of patients with angina pectoris and coronary disease was available in this clinic. Most of these patients were followed by Drs. Riseman and Brown and the diagnoses of angina pectoris were confirmed by exercise tolerance tests²². The duration of the disease, in every patient on whom lipid studies were made, was more than one year. Approximately one-third of the group gave a history consistent with cardiac infarction in the past. Patients with rheumatic and syphilitic heart disease were excluded. All were ambulatory, and at the time blood samples were taken, they were not suffering from any of the usual cardiac complications, such as acute coronary thrombosis, or circulatory failure. Those selected for this study were likewise free from other complications that might alter the lipid metabolism, such as myxedema, diabetes, or

nephritis There had been no departure from their usual diets, and no obvious changes in weight The majority of patients had been on some form of medication such as aminophyllin or small doses of nitroglycerine Ten of the 59 patients studied were female The ages in the entire group varied from 38 to 69 with a mean of 55 years

Selection of Controls The selection of controls presented a problem To insure a low incidence of atheromatosis, one would naturally choose very young adults On the other hand such a selection might be held unsatisfactory because of the possibility of lipid and cholesterol values increasing with age It has been shown, however, that the distribution of the lipid values in older individuals is the same as in young adults²³ Our controls were healthy individuals chosen from among the students, physicians, and workers of the hospital Subjects in both lower and upper age groups were included The ages in this group of 54 subjects varied from 18 to 69 with an average of 34 years In 28 of these in whom more complete blood lipid studies were made, the average age was 42 and 14 of these were above the age of forty-five

RESULTS

Total Blood Cholesterol The cholesterol values by the colorimetric method in 59 patients with angina, and in 54 normal controls are shown in table 1 More values in the higher range are noted in the angina group Thirty-five patients, as against 16 in the control group, showed values above 250 mg The highest cholesterol in the control group was 287 mg while in the angina group there were 13 patients with values above 287 mg Figure 1 shows the distribution of these values expressed in per cent of total cases The values obtained in patients with angina pectoris are seen to taper off slowly with a spread considerably beyond the control values The mean for the angina patients is 260 mg \pm 6.9, the mean for the control group 218 mg \pm 5.4, the difference 42.0 mg \pm 8.8 (Table 3)

Table 2 gives the cholesterol values by the gravimetric method in 32 patients with angina pectoris and in 22 controls More of the values in the angina group, as measured by this method, are also in the higher range Eighteen of 32 values in patients with angina, or 56 per cent, were above 250 mg while in the normal group only five or 22 per cent of 22 values were above 250 mg There were 12 values in the anginal group above 282 mg, the highest normal cholesterol The distribution of these values is shown in figure 2 The mean cholesterol for the angina group is 259 mg \pm 10.2, the mean for the control group 219 \pm 8.7, the difference, 40 \pm 16.7 (Table 4)

Free Cholesterol A comparison of the values for free cholesterol in 31 patients with angina and 16 normal controls (table 2) shows again a higher average value for the former Twenty-one of the 31 values were 80 mg or above, as against five out of 16 normal controls above 80 mg

TABLE I
A Comparison of the Fasting Blood Cholesterol* in Patients
with Angina Pectoris and in Normals

Angina Pectoris					Normals				
Case No	Age	Sex	B M R % deviation from the normal	Cholesterol mg /100 c c	Case No	Age	Sex	B M R % deviation from the normal	Cholesterol mg /100 c c
1	57	M	-7	119	1	54	M		131
2	66	M	+11	184	2	26	F	+12	145
3	57	F	-10	185	3	53	M		150
4	57	M	-10	190	4	52	M		157
5	57	M	-24	192	5	30	F	-12	160
6	47	F	+2	195	6	20	F	-16	166
7	55	M	+2	200	7	68	M		172
8	50	M		204	8	25	M	-11	173
9	59	M	-8	205	9	22	M		173
10	57	M	-4	211	10	24	M		178
11	51	M	+3	213	11	25	F	-25	180
12	56	F	-2	215	12	49	M		186
13	57	M	-6	217	13	60	M		190
14	54	M	-14	218	14	33	M	+5	192
15	69	M	-1	222	15	24	M	-15	193
16	59	M	-2	223	16	22	F	+2	195
17	58	M	+7	224	17	24	F	-13	197
18	60	M	-20	232	18	22	F	-19	197
19	54	M	-17	236	19	29	M		203
20	53	M	-15	240	20	26	F	-9	204
21	38	F	+1	243	21	25	M	-12	204
22	58	M	-2	244	22	22	M	-6	206
23	58	M	-21	246	23	53	M		207
24	60	M	+6	249	24	20	F	-12	208
25	48	M	-14	251	25	18	F	+1	208
26	54	M	-12	254	26	48	M		209
27	41	M	-19	255	27	28	M	-23	210
28	51	M		256	28	22	M	-6	214
29	41	M		258	29	22	F	-5	216
30	58	M	+14	258	30	48	M		220
31	55	M	-5	262	31	28	M		225
32	63	M	+6	266	32	48	M		236
33	60	M	-10	266	33	30	M		236
34		F	-16	267	34	38	M	-35	237
35	61	M		267	35	25	M	-16	238
36	57	M	-20	267	36	26	M	-17	238
37	60	M	-20	268	37	26	M	-27	244
38	52	F	+3	269	38	62	M		246
39	54	M	+7	270	39	26	M	-4	251
40	55	M	-13	273	40	50	M		251
41	55	M	-23	278	41	25	M	-15	252
42	58	M	-5	279	42	25	F	-4	252
43	50	M	-21	279	43	34	M	-23	253
44	67	M	-4	281	44	55	M		254
45	50	M	+4	282	45	49	F		254
46			-27	283	46	41	M		256
47	56	M	-22	289	47	38	M		264
48	58	F	-23	298	48	54	M		270
49	60	M		303	49	30	M	-21	273
50	50	F	-19	305	50	26	M	-15	275
51	53	M	-12	308	51	26	M	-6	279
52	52	M		312	52	27	M	-20	286
53	56	F	-1	329	53	25	M	-28	286
54	59	M	+11	333	54	33	F	-21	287
55	38	M	-13	350					
56	54	F	-6	362					
57	54	M		368					
58	57	M	-15	380					
59	48	M	-4	413					

* Cholesterols done by colorimetric method (Meyers, Wardell, Ling)

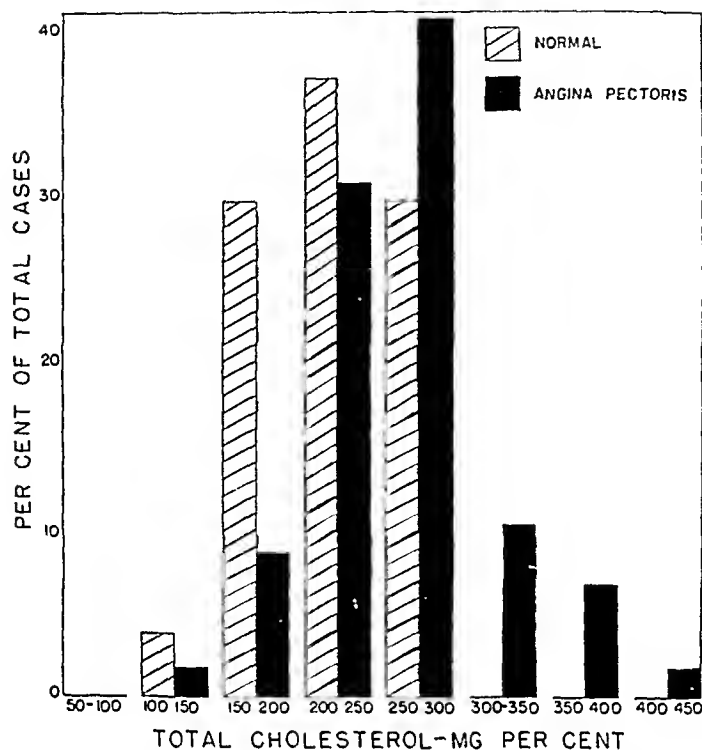


FIG 1 Distribution of total cholesterol in 59 angina pectoris patients and 54 normals
Method of Meyers, Wardell, Ling²⁸

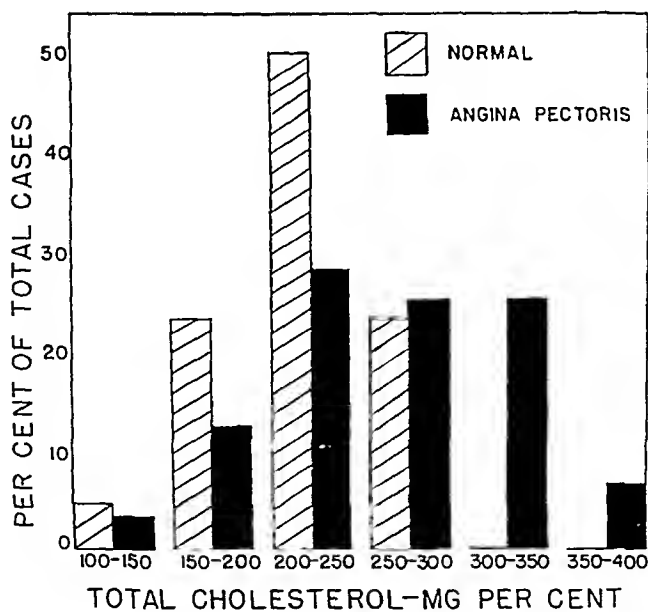


FIG 2 Distribution of total cholesterol in 32 angina pectoris patients and 22 normals
Method of Man and Peters²⁶

TABLE II
A Comparison of the Fasting Cholesterol and Blood Lipids in Patients with Angina Pectoris and in Normals

Angina Pectoris						Normals										
Case No	Age	Sex	Type	Hyper-tension	Lipoid Phosphorus mg/100 c c	Fatty Acids mg/100 c c	Cholesterol		Case No	Age	Sex	Type	Lipoid Phosphorus mg/100 c c	Fatty Acids mg/100 c c	Cholesterol	
							Free mg/100 c c	Total mg/100 c c							Free mg/100 c c	Total mg/100 c c
1	56	M	I	+	100	415	83	222*	1	68	M	L	83	268	48*	173*
2	60	M	I	+	109	444	76	278	2	47	M	P	81	380	74	171
					102	372		3	52	M	L	93	308			
3	58	M	P	0	94	420	91	230	4	60	M	P	82	252	64	194
					108	456		5	41	M	I	110	494			
4	59	M	P	0	139	359	85	290*	6	35	M	I	93	468	38	101
					107	436		7	33	M	L	86	281			
5	53	M	I	0	107	454	80	304	8	30	M	I	101	450	68	257
					109	466*		9	22	M	L	71	243			
6	48	M	P	++	109	417	85	270	10	24	M	L	51	134	67	206
					154	570		11	53	M	L	98	398			
7	59	M	I	0	102	502	90*	355	12	53	M	L	90	302	71*	194*
					107	450		13	23	M	P	77	279			
8	63	M	I	+	108	617	82	304	14	49	F	P	80	345	88	270
					113	594		15	53	M	L	98	463			
9	56	M	I	++	114	462	76	264	16	62	M	P	104	444	89	258
					111	560		17	54	M	P	93	414			
10	60	M	I	0	111	345	103	178	18	53	M	P	119	457	88	270
					112	392		19	55	M	P	76	47			
11	54	M	I	0	112	428	95	239	20	46	M	P	109	516	83	267
					100	300		21	52	M	P	114	480			
12	59	M	I	0	128	392		300	22	36	M	I	86	345	89	258
					141	210		23	29	M	P	108	359			
13	46	F	L	0	141	416		296	24	27	M	P	86	401		
					141	392		25	38	M	P	86	401			

TABLE II—Continued

Angina Pectoris										Normals							
Case No	Age	Sex	Type	Hyper-tension	Lipoid Phosphorus mg/100 c c	Fatty Acids mg/100 c c	Cholesterol		Total mg/100 c c	Case No	Age	Sex	Type	Lipoid Phosphorus mg/100 c c	Fatty Acids mg/100 c c	Cholesterol	
							Free mg/100 c c	Total mg/100 c c								Free mg/100 c c	Total mg/100 c c
16	58	M	P	0	11.1	416	85	281	281	26	23	M	L	10.2	278	69	218
17	66	M	I	0	10.3	304		110	110	27	39	M	P	12.2	328	64	215
18	66	M	I	0	16.6		114	260	260	28	29	M	P	11.4	349	86	282
19	51	M		+	10.5	662											
					13.9	441	76	208	208								
20	51	M		0	8.1	393	73	150	150								
21	58	M	P	0	8.5	352	66	181	181								
22	54	M	I	0	11.0	422											
23	55	M	P	0	9.6	410	89	220	220								
					8.6	380											
24	41	M	L	0	8.7	277	70	242	242								
25	69	M	L	++	10.5	438	85	243*	243*								
26	56	F	P	+	10.4	440	74	219	219								
					10.2	483	84										
					11.6	347	80	236*	236*								
27	51	M	P	0	12.5	548	97										
28	55	M	P	++	12.5	435	105	303	303								
29	61	M	L	0	12.0	380	88	312	312								
30	54	F	I	+	14.9	487	115	340	340								
31	31	M	I	0	9.9	238	70	184	184								
32	67	M	I	0	11.4	409	95	321	321								
33	38	M	L	0	12.6	409	114	350	350								
34	52	M	P	0	11.4	370	97	328	328								
35	50	M	P	0	8.9	366	69	220	220								

* Analysis not in duplicate
P Pyknic
L Leptosome
I Intermediary

Hypertension none—0
slight—+
moderate—++
marked—+++

* Analysis not in duplicate

P Pyknic

L Leptosomic

I Intermediary

Hypertension none—0

slight—++

moderate—+++

marked—++++

There were no values in the control group above 89 mg while in the anginal group there were 13 values above 89 mg. The comparative distribution is seen in figure 3. The mean for the control group is $70.2 \text{ mg} \pm 3.5$, the mean of the anginal group is $86.4 \text{ mg} \pm 2.5$, the difference 16.2 ± 4.3 (Table 3).

Phospholipids Table 3 shows the distribution of the phospholipids as milligrams lipid phosphorus in 34 patients with angina and in 28 normal controls. Twenty-six of 34 values in angina were above 10.0 mg while but 10 of the 28 control values were above 10.0 mg. The highest normal value was 12.2 mg while in the angina group there were seven values above 12.2 mg. Figure 4 shows the distribution of these values, the differences are obviously significant. The means for the anginal and control group are $11.2 \text{ mg} \pm 0.26$, and 9.4 ± 0.30 respectively, with a difference of 1.77 ± 0.40 (Table 3).

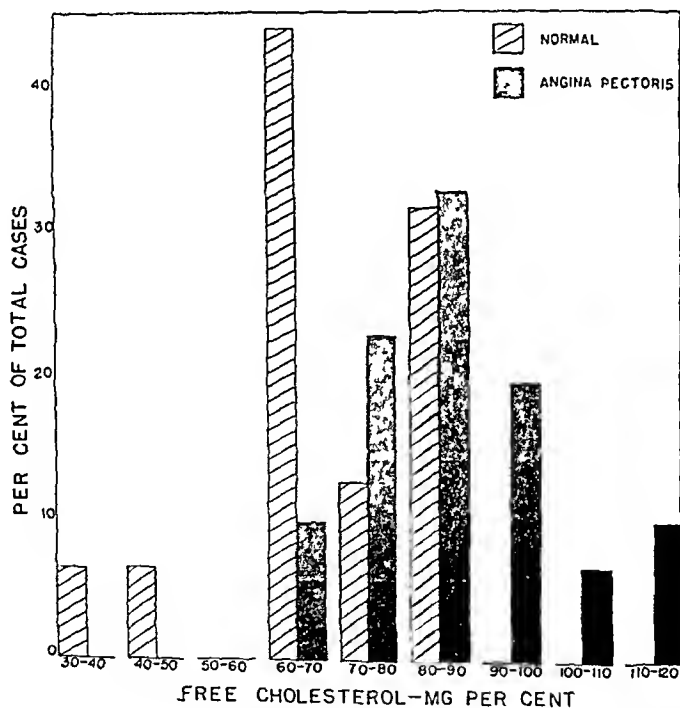


FIG 3 Distribution of free cholesterol in 31 patients with angina pectoris and 16 normals

Fatty Acids A comparison of the fatty acid values in 35 patients with angina, and in 28 normal controls is shown in table 3. Figure 5 shows a tendency toward higher values in the patients with angina for this lipid also. The differences are not so marked as in the case of cholesterol and phospholipids. The mean for the normal fatty acids is $369 \text{ mg} \pm 18.1$, for the anginal group, $429 \text{ mg} \pm 13.7$, the difference 60 ± 22.7 .

Summary of Statistical Analysis of Data In table 3 the values of the several lipid constituents of the blood of patients with angina are com

TABLE III
Summary of Statistical Analysis of Data*

	M mg per cent	S	S _m	D	S _d	D/S _d	P
Total cholesterol colorimetric							
Normal	218	39.8	5.4				
Angina pectoris	260	53.2	6.9	42.0	8.8	4.8	.001
Total cholesterol gravimetric							
Normal	219	40.6	8.7				
Angina pectoris	259	57.5	10.2	40.0	16.7	2.4	1.6
Free cholesterol							
Normal	70.2	13.9	3.5				
Angina pectoris	86.4	14.1	2.5	16.2	4.3	3.8	.015
Fatty acids							
Normal	369	95.5	18.1				
Angina pectoris	429	81.3	13.7	60.0	22.7	2.6	1.6
Lipoid phosphorus							
Normal	9.4	1.61	0.30				
Angina pectoris	11.2	1.52	0.26	1.77	0.4	4.5	.002

* When two or more measurements were made in a given patient, the average value was utilized in computation

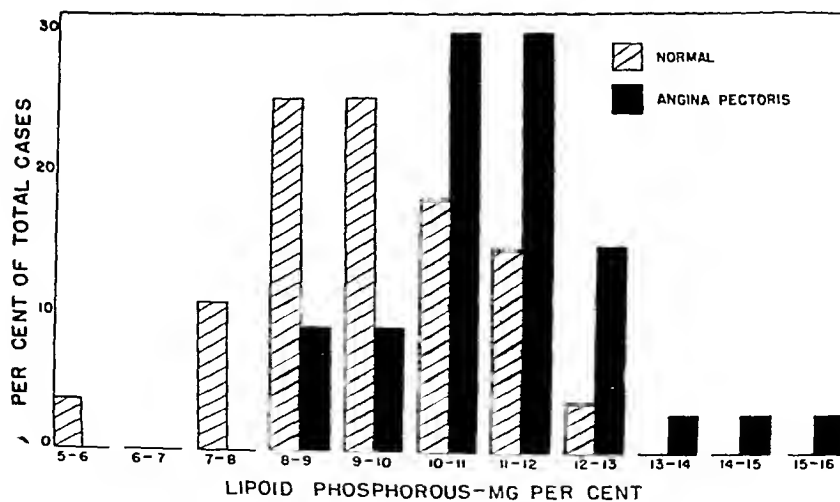


FIG 4 Distribution of lipoid phosphorus in 34 angina pectoris patients and 28 normals

pared with the values in the normal control group. The column M gives the arithmetic mean of the determined values. The column S gives the standard deviation of the series calculated according to the formula $S = \sqrt{\sum D^2 / N - 1}$ where $\sum D^2$ is the sum of the squares of the differences of the individual values from the mean value and N is the number of cases. The column S_m gives the standard deviation of the mean and is equal to S/\sqrt{N} or $\sqrt{\sum D^2 / N(N-1)}$. The column D gives the difference between the mean of the angina group and the normal group. The column S_d gives the standard deviation of that difference which is equal to the square root of the sum of the squares of the standard deviations of the

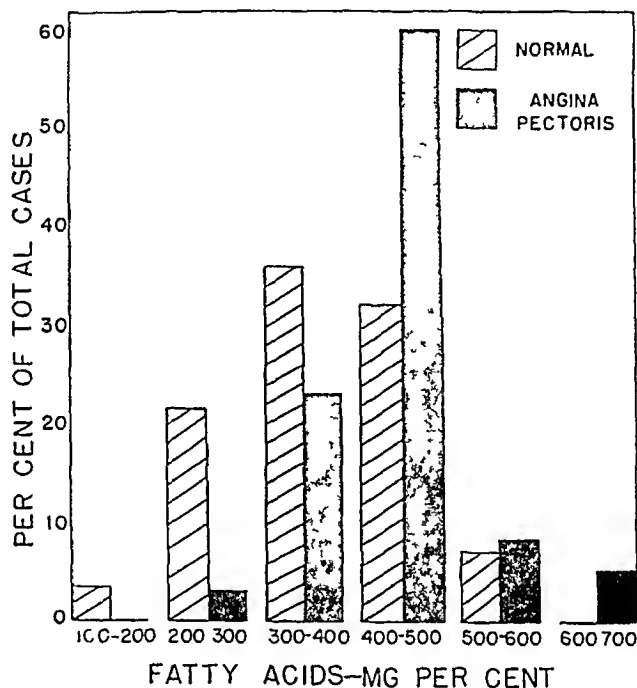


FIG 5 Distribution of fatty acids in 35 angina pectoris patients and 28 normals

respective two means. The column D/S_d gives the ratio of the difference to its standard deviation. In general, values of the ratio above two are considered probably significant and values above three practically certainly significant. Column P gives the probability of a difference as great or greater than the one listed, being due purely to chance. A value of P of 1.0 indicates a probability of 1 per cent or one chance in 100 of the difference being due to a sampling error.

The Normal Values Man and Gildea²⁴ recently studied the blood lipid values in a group of normals. In 76 healthy individuals the mean of the cholesterol values was 196.8 ± 4.0 , 22.1 mg lower than the mean in our control series. This difference is probably significant. Their phospholipid

values were close to ours with D/S_a less than one, although our values were 3 to 5 per cent higher

Gildea, Kahn, and Man²⁵ make the interesting observation that in males the normal lipid values are higher in those with a pyknic and lower in those with a leptosome type of constitution. The pyknic type refers to the stocky individual of short or middle height, rounded figure, broad face and large rounded head on a short massive neck, the leptosome or asthenic, to those with opposite attributes such as greater development of extremities, narrower trunk, longer neck and oval face. The incidence of pyknic types in our small group of 22 normals was slightly higher than in their normals. The proportion of Jews was small in their normals, whereas in our series they comprised half. The cholesterol values of 13 of these Russian-Jewish normals gave an average of 235 mg, the average of nine Gentiles was 193 mg. Eliminating one value of 101 mg in the latter group, which was extremely low, the average was 212 mg. The ratio of the difference between the two means of Jew and Gentile (with the low value of 101 eliminated from the Gentile group) to its standard deviation is 1.69. The probability of such a deviation being due purely to chance is 9.1 out of 100. The phospholipid difference in 14 Jews and 11 Gentiles was similar $D/S_D = 1.74$, and the same was true of the fatty acids to a lesser degree, $D/S_D = 1.43$. These differences raise the possibility of differences due to race. In the group, however, of 59 patients with angina and 54 normal controls which we studied by the Meyers and Waidell method there were three and 14 Gentile subjects respectively. Racial influence, if it exists, was therefore unimportant in our comparisons.

It will be noted that the controls include subjects in both the lower and upper age groups. It has been shown by Page, Kirk, Lewis, Thompson, and Van Slyke²³ that blood lipids and cholesterol values of individuals in different age groups are essentially the same. Our data, as far as they go, are in conformity with this important finding. For example, the average cholesterol of 27 normal individuals below the age of 30 is 215 mg (table 1) as compared with an average of 218 mg for the entire group of fifty-four. Also in nine normals above the age of 50 (table 2) the mean cholesterol measured by the gravimetric method was 214 mg as compared with 219 mg for the entire group of twenty-two. It is of further interest in this connection that measurements made in a few normal subjects at intervals over a period of approximately three years reveal an individual tendency to maintain a rather constant general level of blood cholesterol.

The Inter-relationship of Lipid Fractions, the Ratio of Free to Total Cholesterol. The inter-relationship of the lipid constituents can be seen in table 2. Although there are a number of exceptions, the lipid fractions in the same individual, either normal or angina pectoris, are in a general way proportional to each other. The cholesterol and phospholipid values are more closely proportionate to each other than either of these to the

fatty acid values. A similar proportionality was found in well treated diabetic patients by Man and Peters¹⁶ and in malnutrition by Man and Gildea³⁰. The parallelism of cholesterol and phospholipid values in their series was closer than in ours.

The ratio of free to total cholesterol (figure 6) appeared to be fairly constant for both the normal and the angina groups with a free cholesterol value ranging from 27 to 44 per cent of the total. The mean of the free cholesterol percentages of the totals in the normal group is 32.3 per cent, in the angina group 33.4 per cent. These findings agree fairly closely with those of Page, Kirk, Lewis, Thompson, and Van Slyke²³ who found in normals that the mean of the free to total cholesterol ratios was approximately 37 per cent. In a recent study of 91 healthy adults, Sperry²⁶ using his own method found an average ratio of 26.9 per cent with a maximum of 30.1 per cent and a minimum of 24.3 per cent.

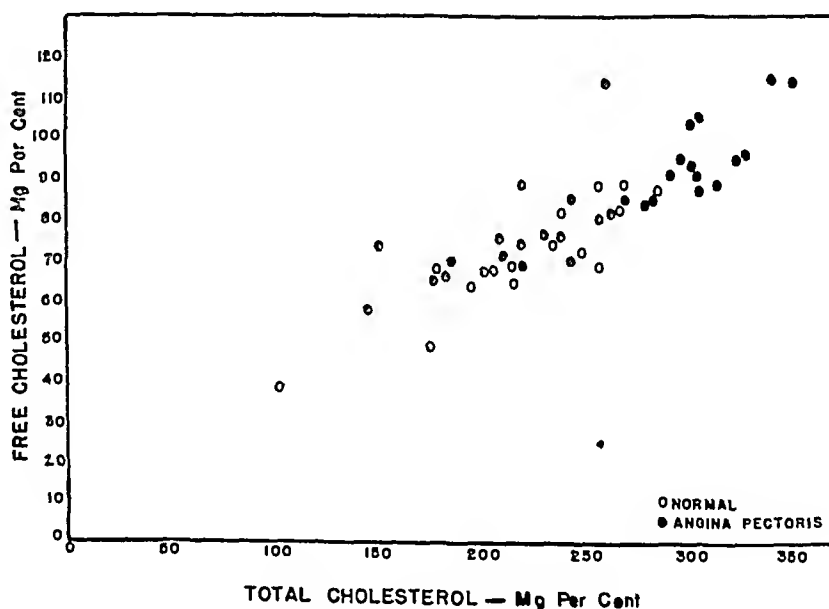


FIG 6 The ratio of free to total cholesterol in 32 patients with angina pectoris and in 16 normal controls

Relation to Basal Metabolic Rate and Hypertension To rule out any possible influence of a preponderance of low metabolic rates in one group or another, the average metabolic rates were considered (table 1). The average basal metabolic rate for 52 patients with angina was minus 8 per cent, for 32 controls minus 13 per cent. The higher incidence of basal metabolic rate values of minus 20 per cent or below in both groups is noteworthy in the absence of clinical hypothyroidism.

In table 2, the presence and degree of hypertension in the patients with angina pectoris are recorded. One plus represents a systolic pressure of 160

to 180 mm or a diastolic of 95 to 100 mm, two plus, a systolic of 180 to 200 mm, or a diastolic of 100 to 110 mm, and three plus, a systolic above 200 or a diastolic above 110 mm of mercury. It will be observed that only four of 34 patients showed moderate or marked hypertension (table 2). Hypertension, generally mild, was present in 13 patients or in 38 per cent. The average cholesterol and phospholipid values of these 13 patients were 266 mg and 11.6 mg respectively. The average cholesterol of 18 and the average phospholipids of 20 patients, both groups without hypertension, were 251 and 10.8 mg respectively. It is obvious that these slight differences are not significant and that the elevated values obtained were not related to hypertension.

DISCUSSION

An analysis of the data presented indicates that the blood lipids are frequently elevated in patients with angina pectoris of atherosclerotic origin. Increases were noted in all the lipid fractions: cholesterol, free and total, lipid phosphorus and fatty acids. These increases are probably more significant than is apparent, in view of the fact that an appreciable percentage of normals have or will develop coronary atherosclerosis. The differences noted obviously applied only to groups. As evidenced in figures 1 to 5, there was considerable overlapping of the values in the patients with angina and those in the control group. It is apparent that lipid values are normal in a large group of patients with angina pectoris. The occurrence of definitely elevated values in some, however, suggests that the lipid and cholesterol metabolism is disturbed either primarily or secondarily in at least a certain group of patients with angina pectoris.

When rheumatic and syphilitic heart diseases are excluded, angina pectoris is, in the majority of instances, associated with coronary atherosclerosis. Stocks²⁷ states, for example, that a reasonable and conservative estimate of the incidence of atherosclerosis of the coronary arteries in patients with angina pectoris is 85 per cent. To obtain further data on this question an analysis was made of 36 necropsy protocols where angina pectoris of arteriosclerotic origin was the clinical diagnosis. Thirty-two or 89 per cent of these patients showed a moderate or marked degree of atherosclerosis of the coronary arteries.

Although there are notable exceptions, coronary atherosclerosis is usually associated with generalized changes of the same kind in the aorta and other vessels of the body. Saphir, Priest, Hamburger, and Katz,²⁸ for example, found moderate or severe general arteriosclerosis in every one of a group of 34 patients with coronary arteriosclerosis and infarction. This would imply that the lipid findings in angina pectoris are in some measure true for general arteriosclerosis.

CONCLUSION

The average cholesterol, free and total, lipid phosphorus and fatty acids of a group of patients with angina pectoris of atherosclerotic origin were found higher than in a group of control subjects. There was considerable overlapping with the values of many angina patients in the normal range. A small group with angina pectoris showed values well above the highest normal value.

We wish to thank Marie C. Volk and Edward S. Glasser for their technical assistance in this investigation.

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THE SIGNIFICANCE OF CARDIAC ENLARGEMENT CAUSED BY ARTERIOVENOUS FISTULA *

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FOLLOWING the establishment of a fistulous connection between an artery and a vein, there occur changes in the dynamics of the circulation which result in varying degrees of cardiac enlargement and of dilatation of the involved artery and vein proximal to the fistula. The extent of the changes depends mainly upon the size of the vessels involved and the caliber of the fistula ¹

In 1924 Holman ¹ expressed the opinion that the dilatation of the proximal artery and vein was an adjustment mechanism for the accommodation of the increased volume of blood flowing through the artery-vein fistulous system. These conclusions are tenable and universally accepted. The causation and the significance of the cardiac enlargement which occurs in association with the vascular changes remained a debatable problem.

From a series of 11 cases of acquired arteriovenous fistula four have been selected for special study because we felt they offered opportunities for the acquisition of fundamental data relevant to the significance of the cardiac enlargement.

1 In three instances the femoral vein and artery were involved at approximately the same anatomical point. The popliteal was involved in the fourth.

2 In one instance the fistula had existed for five weeks, in another eight months, in the third three years and seven months, and in the fourth 21 years.

3 The location of the fistulae made it possible to study the venous pressure and the velocity of venous flow proximal to the fistulous connection.

METHODS USED

All physiologic studies were made three to four hours after the last meal, the patient remaining in bed on these days. The venous pressure was measured by direct venipuncture, using the apparatus and technic of Moritz and von Tabora ². Measurements of the velocity of blood flow were made with the use of the cyanide method of Robb and Weiss ³.

* Presented in abstract at the meeting of the Association of American Physicians, May 4 and 5, 1937. Received for publication June 19, 1937.

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The operations were done by Dr I A Bigger, Chief of the Surgical Staff, Hospital Division, Medical College of Virginia, Richmond, Virginia.

The heart size was determined by the use of teleroentgenograms. These were standardized to constant chest diameters and the position of the diaphragmatic level. The prediction formula of Hodges and Eyster⁴ was used in calculating normal transverse cardiac diameter.

CASE REPORTS

Case 1 S. B., a negro laborer, aged 45, five weeks previously had received a bullet wound in the upper right thigh. He stated that he was working as a laborer 10 days after the accident without subjective complaints or impaired function of the involved limb.

Physical examination A well developed negro man in a normal state of physical fitness. The local phenomena of an arteriovenous fistula were present at the apex of Scarpa's triangle on the right side, indicating a fistulous connection between the right femoral artery and vein.

		Fistula opened	Fistula closed
Blood pressure		systolic 130, diastolic 65	systolic 150, diastolic 100
Pulse rate		79 per minute	62 per minute
Vital lung capacity	predicted normal	5,360 c c	
	actual	5,180 c c	

Electrocardiogram normal, no change following operation. The physiological studies and heart size data before and after operation are shown in figure 1.

Case 2 A. H., a white farmer, aged 32, had received a bullet wound in the upper left thigh three years and seven months previously. He stated that he resumed his farm work two weeks after the accident. He noticed a thrill and swelling over the femoral area a few days after receiving the wound. For the past seven months there had been some swelling of the left foot and ankle. During cold weather this foot became numb and there was aching in the calf muscles of the left leg if he walked rapidly up grade. The subjective complaints were not sufficient to stop him from his work. He came for relief of the functional impairment and swelling in the left leg.

Physical examination A well developed man in a normal state of physical fitness. The local phenomena of an arteriovenous fistula were present 2 cm. below the apex of Scarpa's triangle on the left side indicating a fistulous connection between the left femoral artery and vein. There was slight pitting edema of the left ankle.

		Fistula opened	Fistula closed
Blood pressure		systolic 130, diastolic 55	systolic 140, diastolic 95
Pulse rate		88 per minute	60 per minute
Vital lung capacity	predicted normal	5,100 c c	
	actual	5,300 c c	

Electrocardiogram normal, no change following operation. The physiological studies and heart size data before and after operation are shown in figure 2.

Case 3 A. G., a white boy, aged 16, had received a bullet wound in the left popliteal space eight months previously. Two weeks after the accident he resumed his usual physical activities, consisting of work on a farm and playing baseball whenever he was not otherwise engaged. His only complaint was fatigue and aching of the left leg after strenuous exercise.

Physical examination A robust well developed boy in a normal state of physical fitness. The local phenomena of an arteriovenous fistula were present in the left popliteal space indicating a fistulous connection between the left popliteal artery and

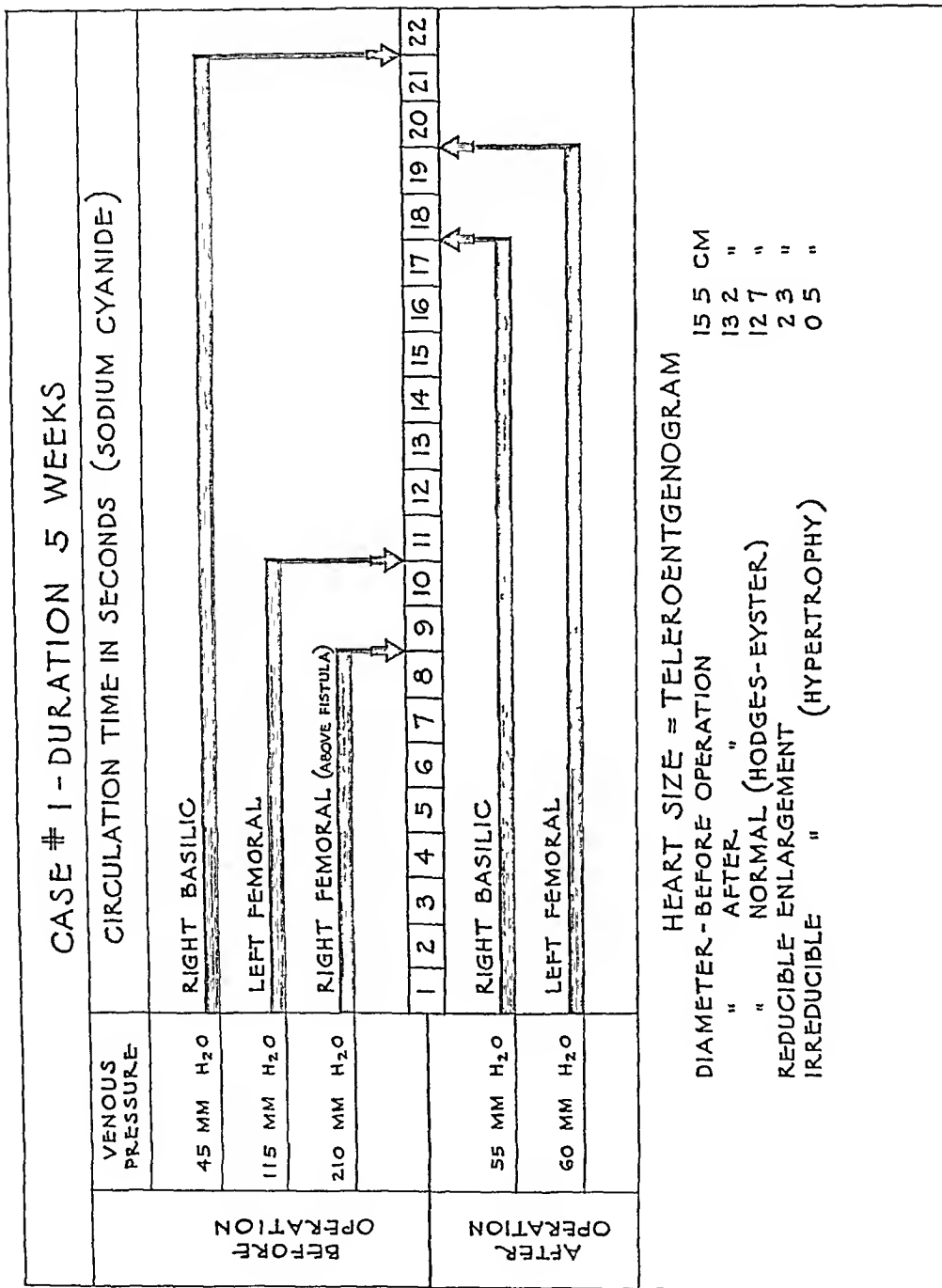


Fig 1 Case 1 Circulation time in seconds and venous pressure in mm of H₂O and heart size before and after operation

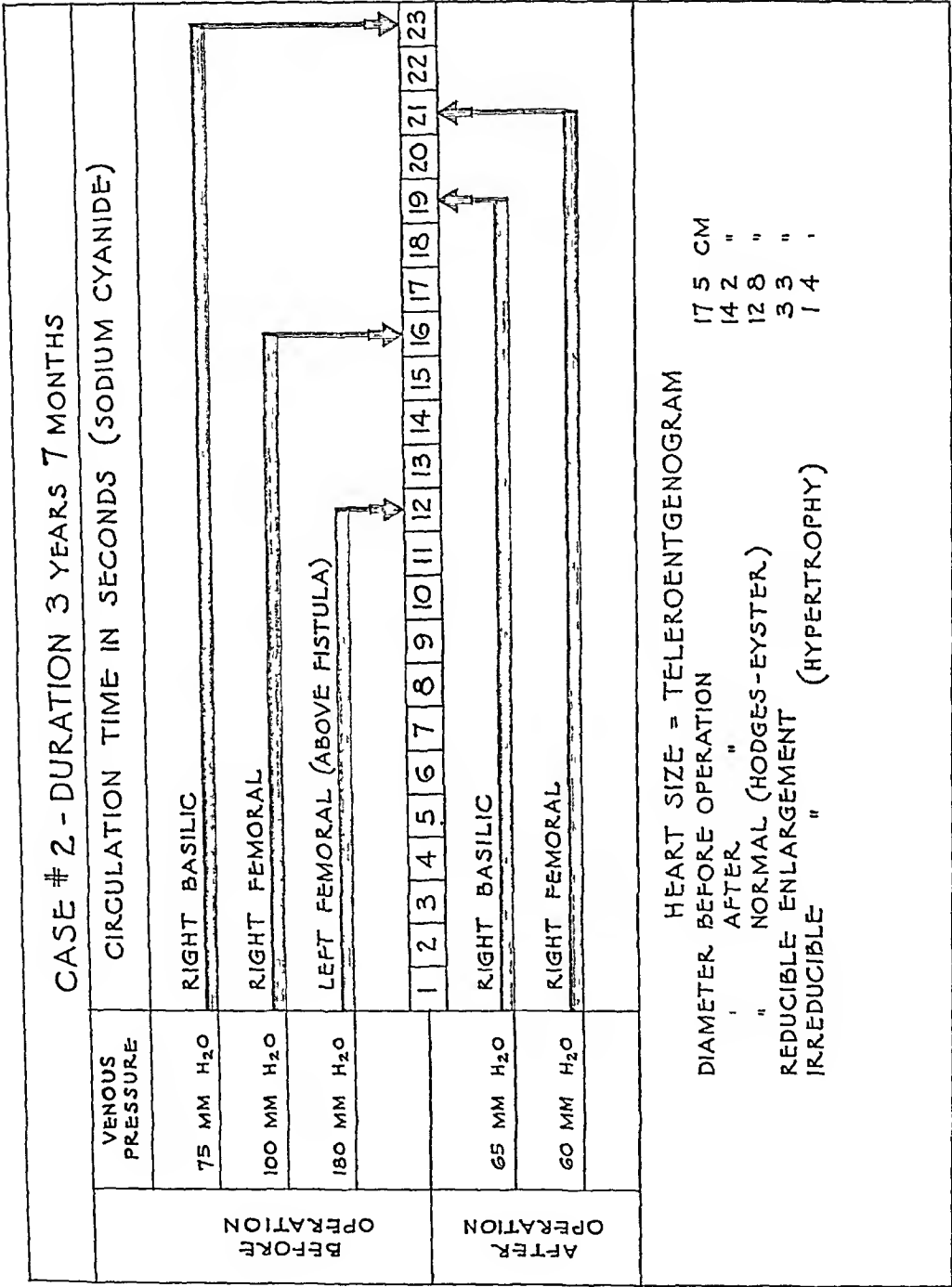


Fig 2 Case 2 Circulation time in seconds and venous pressure in mm of H O and heart size before and after operation

vein The neighboring superficial veins were definitely dilated There was no edema of the left leg or ankle

	Fistula opened	Fistula closed
Blood pressure	systolic 122, diastolic 60	systolic 126, diastolic 75
Pulse rate	90 per minute	76 per minute

Electrocardiogram normal, no change following operation The physiological studies and heart size data before and after operation are shown in figure 3

Case 4 C B, a negro farmer, aged 58, had received a bullet wound in the right thigh 21 years previously Following the accident he remained in bed for 10 days When the dressing was removed he noticed upon touching the upper part of the thigh a peculiar purring sensation which he states has continued and become more distinct Since the healing of the wound he has worked regularly as a farmer with no discomfort except for the occurrence of cramps in the calf muscles of the right leg There had been swelling of the right foot and leg for four years He came for relief of the functional impairment and swelling of the right leg

Physical examination A well developed and nourished negro man lying comfortably in bed without subjective complaints The local phenomena of an arteriovenous fistula were present 3 cm below the apex of Scarpa's triangle on the right side indicating a fistulous connection between the right femoral artery and vein There was a moderate degree of brawny edema up to the upper third of the right leg The vessels above the fistula were greatly enlarged as far as they were palpable The jugular bulb on the right side was markedly dilated but there were no pulsations above the auricular level There were no phenomena indicating heart failure of the congestive type

	Fistula opened	Fistula closed
Blood pressure	systolic 130, diastolic 65	systolic 146, diastolic 94
Pulse rate	84 per minute	56 per minute

Electrocardiogram normal, no change following operation Venous pressure and heart size data before and after operation are shown in figure 4

DISCUSSION

It is evident from these studies that cardiac dilatation is the principal factor concerned in the increase in cardiac size in arteriovenous fistula The amount of actual hypertrophy is determined mainly by the duration of the fistulous connection (figure 5)

Lewis and Drury^{1, b} concluded that the enlargement of the heart was primarily and chiefly a dilatation due to a deficient nutrition of the heart muscle, consequent on a fall of the mean arterial blood pressure occurring in arteriovenous fistulae They did not believe there was increased circulating blood volume for in experiments on dogs an anastomosis of an artery and vein did not increase cardiac output unless there was a rise in general venous pressure, and no rise in general venous pressure occurs in arteriovenous fistulae without heart failure Recently Laplace⁵ and Quattlebaum⁶ have expressed opinions in agreement with that concept of the pathogenesis of cardiac enlargement

It is an established physiologic principle that the minute volume of cardiac output is dependent primarily upon the volume of the return flow to

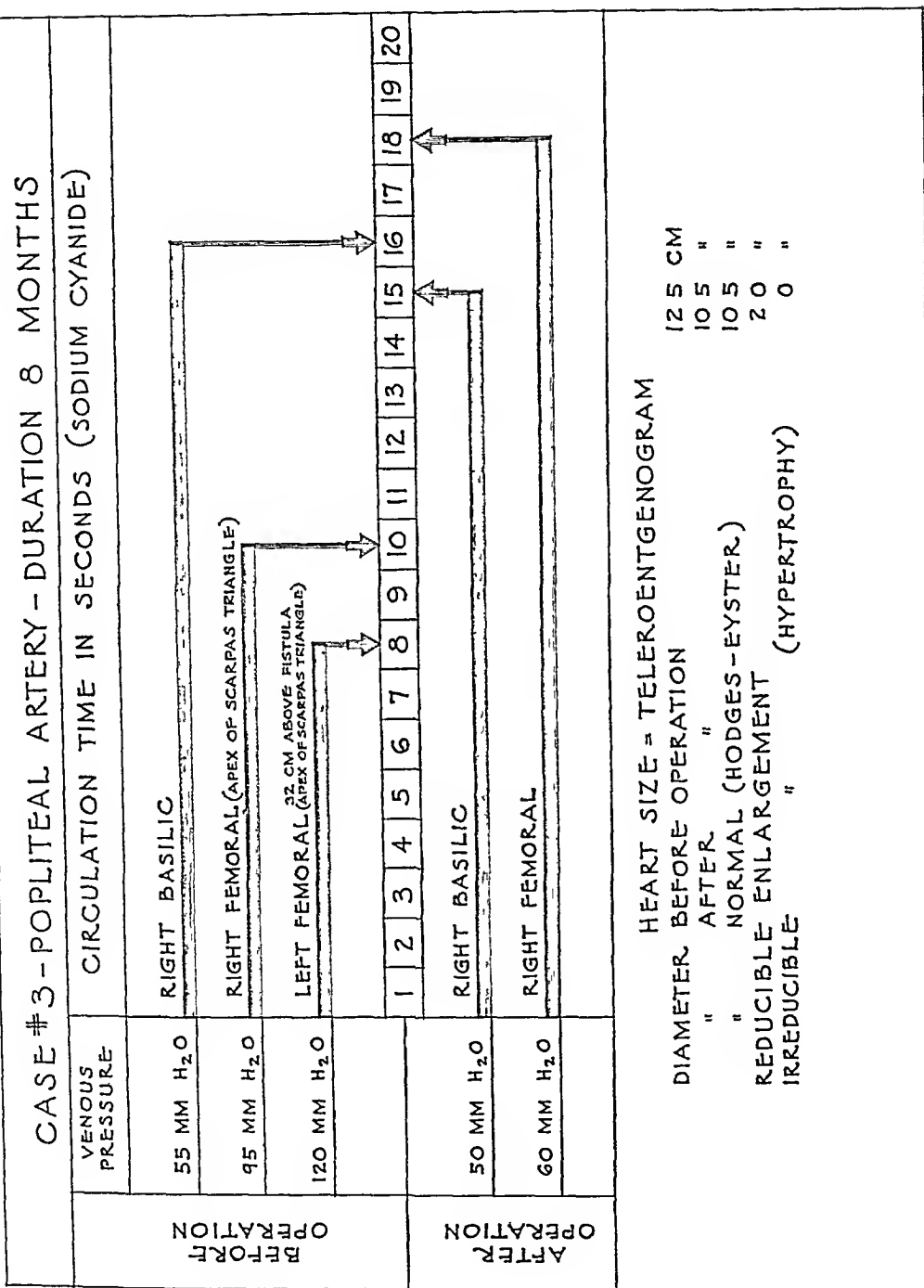


Fig 3 Case 3 Circulation time in seconds and venous pressure in mm of H₂O and heart size before and after operation The femoral vein was used at a point corresponding approximately to a similar location as that in Cases 1 and 2

the right auricle, and the force of cardiac contraction is so perfectly adjusted to the quantity of blood which flows into the auricle from the veins that no stasis occurs with a rise of general venous pressure unless heart failure ensues

The observations made on these patients show that all the factors which can increase the volume of return flow to the right heart operate in arteriovenous fistulae, and in these patients without heart failure there was no rise of general venous pressure

That the dilatation of the heart is not due to a nutritional deficit of the myocardium is evident from the cases here studied. It is inconceivable that a nutritional factor could be responsible for so marked a degree of reducible dilatation continuing for a long period * and without the development of heart failure in men engaged in active physical labor. Furthermore, Green ⁷ has shown that in arteriovenous fistulae the decrease of coronary blood flow induced by a lowering of diastolic blood pressure is to a considerable extent mitigated by an increase in coronary blood flow during systole resulting from a relative lowering of the systolic peripheral coronary resistance in relation to aortic pressure. Through peripheral vascular constriction a normal mean blood pressure may be approximated and this, operating in conjunction with the augmented systolic coronary circulation, may result in an increase of coronary flow to or even above a normal minute volume.

The observations made on these patients indicate that the cardiac enlargement occurring in arteriovenous fistulae results from the following changes in the dynamics of the circulation

1 (a) There is great increase in cardiac filling due to acceleration of the velocity of blood flow and increase of effective venous pressure in the involved vein and anatomically associated tributaries proximal to the fistulous connection

(b) With adjustment dilatation of the artery and vein the rate of blood flow and the pressure in the vein decrease while the cross section of the column of the returning current increases

(c) The enlargement of the artery and vein in the fistulous circuit and the increase in cardiac size are primarily an adjustment dilatation. Cardiac hypertrophy is responsible for only a small part of the increase in cardiac size

2 An extreme degree of reducible cardiac dilatation, 21 cm to 15.2 cm, can exist over a prolonged period (21 years) with the occurrence of only a minimum amount of cardiac hypertrophy and without the development of heart failure. This is not in agreement with the concept of a myocardial nutritional defect as the factor responsible for the changes in cardiac size

* In this connection the observations made on Case 1 are of interest. The femoral artery was temporarily occluded by ligature. Within 24 hours the cardiac dilatation had reduced from 15.5 cm to 13.4 cm. Due to the ischemic symptoms developing in the foot, the ligature was removed. Within 24 hours thereafter the heart again measured 15.5 cm.

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CONGENITAL ADHESIONS OF THE GALL- BLADDER ¹

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ABNORMAL peritoneal attachments to the gall-bladder are more common than inflammatory adhesions. Though often described these congenital adhesions ¹ are not generally recognized, so strong is the obsession in the medical profession that all disturbances of the gall-bladder are inflammatory in origin. Yet, it should be obvious to the careful observer that these sheets of tissue, running from lesser omentum to gall-bladder, duodenum and colon, are simple folds of peritoneum having definite relations, definite structure, and regular arrangement of vessels. They cannot possibly be the result of inflammation. Often with these attachments there is no evidence of a past infection of the gall-bladder, in fact, many times the vesicle appears normal.

Inflammation as a result of infection has been over emphasized in pathological conditions of the gall-bladder—considered primary to everything—especially to gall-stones. Anatomical, mechanical and metabolic factors have been neglected. Even cholesterosis confined to the mucosa of the gall-bladder has been attributed to infection, though this is no more likely to be true than with atherosclerosis. It is probable that they are both degenerative diseases, from toxic or metabolic disturbance, with inflammatory effects.

There are two ways of determining whether or not the peritoneal attachments under discussion are congenital or inflammatory adhesions. The first, and most important, is their anatomical relations. The second is lack of evidence of inflammation in the gall-bladder itself.

Embryologically, the development of abnormal peritoneal attachments of the gall-bladder appears fairly simple. The primitive digestive tube has an anterior and a posterior mesentery. In rotation of the stomach the posterior mesentery becomes the greater omentum, and the anterior, the lesser omentum. In the anterior mesentery a bud grows out from the enteric tube to form the liver, bile ducts and gall-bladder. Ordinarily the anterior mesentery stops at the common bile duct and portal vessels, but it may be more extensive and run from the common duct laterally over to the gall-bladder, down to the duodenum, and to the hepatic flexure of the colon—even to the right lobe of the liver and to the lateral and posterior abdominal walls, perhaps closing the foramen of Winslow. There may be

* Received for publication April 16, 1937

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much or little of this anterior mesentery, from a slight band of tissue running from the lesser omentum across to the cystic duct and down the front of the gall-bladder, to the extensive sheet of tissue described above. On this sheet may become a loose veil with a mesentery to the gall-bladder, which means simply that the gall-bladder is enfolded and supported in the tissue. The sheet may be closely adherent to the gall-bladder over its surface or there may be two separate sheets, one running to the medial and one to the lateral margin of the vesicle, usually attaching to the liver on either side. The sheet may pass over the gall-bladder without attachment. The tissue may be absent above and below, leaving only a band from the lesser omentum across the duodenum to the anterior surface of the gall-bladder. It may be supplemented by another distinct band to the hepatic flexure of the colon. In all these types the general relations are the same except that different parts of the sheet of tissue may be missing.

Meyers and Bloom² in 1933, made a study of these congenital peritoneal adhesions in the upper right quadrant of the abdomen, but while stating that these definite structures described were not of inflammatory origin, they have contributed to the general misunderstanding with regard to their nature by the terms, "periduodenitis" and "pericholecystitis" or "essential periduodenitis". Because of confusion of terms and the frequency of this abnormality, surgeons may be led to make false operative diagnoses in many cases.

A resume of literature by Meyers and Bloom shows that different authors have found, on the average, 20 per cent of abnormal peritoneal attachments about the gall-bladder and duodenum in apparently normal individuals. In 54 cadaver and autopsy specimens they themselves found membranes in 54 per cent. Only 5 per cent showed inflammatory adhesions.

In 51 cadavers examined by the writer at the Boston University School of Medicine definite abnormal peritoneal attachments to the gall-bladder were present in 45 per cent. All of the gall-bladders with these congenital adhesions appeared thin-walled and normal. All except one were in male cadavers. (There were not more than five or six females among the 51 subjects.) This is another fact which weighs against inflammatory origin, since cholecystitis is more common in the female.

Among 100 patients upon whom cholecystectomy was performed by me at the Massachusetts Memorial Hospitals 18 showed definite abnormal peritoneal attachments to the gall-bladder. Fifteen of these 18 patients were women. From a statistical point of view it is doubtful that sex is significant in this condition.

Following is a summary of the anatomical arrangement of congenital peritoneal adhesions in 23 cadavers and in 18 patients.

Twenty-three of 51 cadavers examined had definite congenital adhesions to the gall-bladder and duodenum. In this series the arrangement typical for such attachments prevailed, that is, a sheet of tissue running from the lesser omentum to the gall-bladder, along its border toward the fundus,

with bands running across the duodenum and to the hepatic flexure of the colon. In one case there was a small band about 2 cm. in width from the ampulla of the gall-bladder across the duodenum. All the others had attachments of at least two-thirds the length of the gall-bladder, three of them from the gall-bladder to the duodenum alone, and the other 20 from the gall-bladder to the duodenum and hepatic flexure of the colon. In two of these there were extra strands of peritoneal tissue running from the first and second parts of the duodenum up to the liver, but *in no case was any constriction of the duodenum produced*. In four of the 23 cases the foramen of Winslow was closed. One case with the extensive type of attachment described had, in addition, a short mesentery of the gall-bladder. Jackson's membranes were present in three, which does not show a large relationship with congenital peritoneal adhesions elsewhere. In two cases outside this series the author observed an extensive peritoneal attachment of the hepatic colon to the right lobe of the liver laterally, with none to the gall-bladder. In one other case an attachment ran from the liver to a point at a considerable distance along the transverse colon.

All the gall-bladders of this series in cadavers were thin-walled and apparently not inflammatory. There was one female among 22 males. The instances of inflammatory adhesions in the whole number of 51 were not recorded, but I am sure that there were not over 10—a much lower percentage than that of congenital adhesions.

In 18 patients from a series of a hundred cholecystectomies by the author at the Massachusetts Memorial Hospitals a greater variety of abnormal attachments prevailed.

In five cases there was a peritoneal sheet running the whole length of the gall-bladder, in four this was connected with the duodenum, and in two with the hepatic colon. *In one of these there was moderate constriction of the second portion of the duodenum.* The foramen of Winslow was closed in two.

In four cases there were small attachments running from one-third to one-half way down the gall-bladder. In all of these a band passed over the first or second part of the duodenum, and in one the foramen of Winslow was closed.

In two cases there was a loose veil of tissue running over the whole gall-bladder and attached to duodenum, colon and liver. In these two cases definite mesenteries of the gall-bladder were present. *In one of them there was a short strand running from the duodenal cap to the liver, producing some tension.* In both, the foramen of Winslow was closed.

In five cases there were sheets of tissue running across the gall-bladder at varying distances below the fundus, and attaching to the liver and posterior abdominal wall laterally. Four of these *showed bands running across the duodenum, two of which produced moderate constriction.* In three cases there were attachments to the hepatic flexure of the colon, and in three of the five the foramen of Winslow was closed. The appearance of one

case was described as a "sort of blanket thrown over the gall-bladder with the head and chest sticking out" In another case there was a second sheet running to the postero-lateral margin of the gall-bladder The description here was, "the fundus of the gall-bladder looked almost like the head of a doll protruding from between the upper and lower blankets"

In one of these cases an unusual situation prevailed I quote from the operative note, "Running from the lesser omentum and the first part of the duodenum across the fundus of the gall-bladder to the liver and then on to the second portion of the duodenum and hepatic flexure of the colon was a thin sheet of peritoneum-like tissue This sheet of tissue ran downward, partially closing the foramen of Winslow The arrangement was almost as though the gall-bladder were inside a case of tissue The gall-bladder was not adherent to it and when this tissue was removed the peritoneal covering of the gall-bladder was intact" That there was no inflammation of the peritoneum was obvious when the gall-bladder was removed by dissecting its serosa

In two cases the usual attachment was present, running from the lesser omentum along the gall-bladder from cystic duct to fundus But then it was reflected posteriorly to the liver and abdominal wall, running across the duodenum and attaching to the hepatic flexure of the colon There seemed to be in these two cases two distinct layers of tissue, anterior and posterior, 4 to 5 mm apart, along the attachment to the gall-bladder

DIAGNOSTIC INVESTIGATION

The question as to whether congenital peritoneal attachments to the gall-bladder, duodenum and colon produce definite symptoms is difficult to settle It is important that efforts be made in this direction to throw more light on obscure symptomatology in the right upper quadrant of the abdomen, and to avoid unnecessary surgical interference, yet to be able to advise operation when indicated No definite symptom picture presents itself It may be that this very indefiniteness of the symptoms, such as vague discomfort in the right upper quadrant, anorexia or nausea, bloating, "sour stomach," or occasional sharp twinges of pain unrelated to meals, or perhaps increased following meals, are indications of anatomical disadvantages which prevent normal function

Homans³ who has made a careful study of symptomatology in 11 cases of "congenital transduodenal bands" has grouped symptoms under the headings of "intermittency," "food relief," "vomiting" and "bleeding" In his 11 cases, five had intermissions, some discomfort being more or less steadily present Six of the cases showed a definite food relief, but in others taking of food excited discomfort Vomiting was present in six of the 11 cases In none was there a history of hematemesis

In Homans' cases gastric analysis was of no value, some showing high and some showing low acidity

Roentgen-rays in three of nine cases of Homans which were studied showed duodenal defects, two, dilatations of the upper duodenum, one, hour-glass stomach. In one, hyperperistalsis was present, and in another, an atonic stomach.

Homans' cases were diagnosed as everything else than "transduodenal bands," the question of this diagnosis being brought up in only two of them. The most common confusions were duodenal ulcer and chronic cholecystitis. Three of Homans' cases were neurotic.

Meyers and Bloom believe that for diagnosis combined examination of the gall-bladder and the gastrointestinal tract is of no advantage, and hold that fluoroscopy is not practical on account of failure of visualization of the gall-bladder. They attribute significance to a "shifting deformity" of "Duval." "Duval deformity is differentiated from ulcer deformity in that the latter is constant in any one segment of the cap, whereas the former is shifting. Duval's deformity is differentiated from irritable cap in that with the former the cap is filled but the deformity occupies a varying segment of the cap and is still irregular after atropine." The impression of Meyers and Bloom is that no clinical entity can be built up from the symptoms in these cases and that periduodenal adhesions of this type are not significant clinically.

In the study of the symptomatology in my series, seven of the cases had to be ruled out on account of the presence of gall-stones, leaving 11 for study.

In two of the 11 cases the duodenum was deranged somewhat, in one of these the first part was pulled up by a short strand running to the liver, in the other there was a slight constriction at the second part. Both of these cases had more or less discomfort in the epigastrium and right upper quadrant after meals, with nausea and vomiting. Both were subject to migraine. One of the two was relieved considerably by cholecystectomy and section of the adhesions, but the other was practically unrelieved. They were followed three and five years.

In three of the cases where the gall-bladder was greatly constricted by abnormal sheets of peritoneum running across it, there was discomfort and irregular pain in the right upper quadrant associated with more or less nausea and vomiting, the pain being worse after meals. Following removal of the gall-bladder and congenital adhesions in these cases, symptomatic relief was obtained after an average period of one month. This has lasted for two years in two of the cases. The other patient could not be located for follow-up.

In the two cases where a loose veil covered the gall-bladder with a mesentery, relief for three and five years was obtained after removal of the vesicle.

With four cases in which the abnormal attachments were of lesser extent, and there were symptoms of gas, indigestion, feeling of fullness with epigastric discomfort after meals, removal of the gall-bladder and adhesions

gave relief in one for three years. One, who had been subject to migraine was unrelieved after three years, two who were neurotic were unrelieved after several months.

From the above records it will be seen that relief appeared to follow operation in those cases where the gall-bladder was restricted in its motion by the congenital adhesions or where the motion was abnormally free through a mesentery. The possibility with the hypermobile vesicle is that kinking of the cystic duct interfered with emptying. In one of the two cases with mesentery a transverse constriction of the gall-bladder was shown by the Graham test, although emptying was only slightly delayed, but in the other the gall-bladder was exceedingly large and emptied abnormally slowly.

Although Meyers and Bloom do not believe that *fluoroscopy* is of value it seems that this means to aid the diagnosis should not be lightly given up. The combined examination of the gall-bladder and stomach, duodenum and colon has been suggested several times⁴ and some studies have been carried out.⁵ If the "double-oral" method of cholecystography is used^{6,7} the gall-bladder in most cases can be visualized under the fluoroscope. If the shadow presents irregularities on the roentgenogram, such as apparent pulling of the fundus toward the mid-line, and if there is lack of mobility under the fluoroscope, adhesions are suspected. If under combined examination the gall-bladder, duodenum and hepatic flexure of the colon can not be separated, or are distorted, adhesions are probable. However, with a thick or tense abdominal wall manipulation of the viscera may be so difficult that nothing can be learned in this way. If the shadow of the gall-bladder hangs low or has an unusual alignment, and is hypermobile under the fluoroscope, it may have a mesentery as well as other peritoneal attachments. However, in the 12 cases with congenital adhesions in which stones were absent the diagnosis of "perivesicular" adhesions was made in only two cases. But this was worth attaining and is encouraging to further effort.

THE QUESTION OF TREATMENT

Rational treatment of these congenital right upper quadrant adhesions would depend upon definite diagnosis. If there were only moderate symptoms and a few abnormalities, like "shifting irregularity of the duodenal cap"² or "hypo-mobility" or "hyper-mobility"⁵ of the gall-bladder, medical treatment should certainly be tried first. It appears that a considerable number of these patients are neurotic. The relation here may be that neurotic individuals magnify slight symptoms produced by interference with motility of these organs in their normal physiological activities, or there may be functional disturbances elsewhere such as "irritable colon." These congenital adhesions might in many cases adjust themselves by stretching without an operation. Then, too, it must be remembered when contemplating operation that the postoperative adhesions might be more restrictive than

the congenital On the other hand if the patient has severe symptoms such as inability to hold food on the stomach to a dangerous degree, together with signs of irregularity or torsion of the duodenum or gall-bladder, operation is advisable

In the case where the previous diagnosis has not been made and congenital adhesions are found at operation, the question arises as to what to do. Constricting bands should certainly be relieved. It seems to me that the gall-bladder should be removed also. It is not a necessary organ and in all probability the dire results attributed to its loss have been exaggerated. If for good reason a surgeon exposed my gall-bladder I would thank him to remove it even though it appeared normal, provided of course, it were done with little trauma to abdominal viscera and without damage to the liver. During an operation for the removal of gall-bladder and congenital adhesions it must be kept in mind to leave as little raw surface as possible. In some cases it might be advisable to remove the gall-bladder and then only to relieve restricting bands, allowing a considerable amount of the peritoneal tissue to remain to prevent postoperative adhesions which might occur on surfaces from which it had been removed.

SUMMARY AND CONCLUSIONS

Congenital peritoneal adhesions to the gall-bladder are much more common than is ordinarily realized since they are found in about one-fourth of the population.

That many of these adhesions, or bands, do not produce symptoms is probable, but that some of them do is almost certain.

The symptom picture is hazy. It consists chiefly of vague right upper abdominal discomfort or pain—stabbing or dragging, intermittent or more or less constant—usually worse after meals, and often accompanied by nausea or vomiting. Neurotic symptoms may be prominent.

Preoperative diagnosis is difficult. It depends upon the above symptom picture, the elimination of other causes of right upper quadrant pain, under combined roentgenoscopy, lessened or increased mobility of the gall-bladder in relation to other viscera—perhaps tenderness.

Treatment should be first medical, with a view to reducing the alimentary load for a more or less crippled digestive system, second, psychological.

Surgery should be reserved for those cases where the roentgen-ray, including fluoroscopy, shows abnormalities, where other measures fail, and where pain and/or nausea and vomiting are severe.

Operative treatment consists in removal of the gall-bladder and section of constrictive bands or sheets of peritoneal tissue. Care must be taken to prevent secondary adhesions, or these may become more troublesome than the primary.

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SAMUEL JONES GEE AND HIS FRIENDS *

By SIR HUMPHRY ROLLESTON, Bt, G C V O, K C B

PERHAPS the best way I can join in a tribute to Joseph Hersey Pratt—the clinical physician—is to offer a sketch of another clinical physician, at St Bartholomew's Hospital, with some sidelights on contemporary medical London when I was a student there half a century ago. The names of great physicians have often been linked by their admirers with recently recognized forms of disease, and also with favourite prescriptions—the least of their achievements. Samuel Jones Gee is an example of this eponymous association. Fifty years ago what is now known as posterior basal meningitis or, as Still showed in 1898, chronic meningococcal meningitis of infants was colloquially known in London as "Gee and Barlow's disease" after their account in 1878 of cervical opisthotonos in infants which in his aphorisms Gee later summarized as follows "not a tuberculous affection, it is due to a chronic meningitis of the medulla. It may, however, occur as a symptom in tuberculous affections of this region." In 1899 Sir Thomas Barlow (1845–) and David Bridge Lees (1846–1915) gave an expanded account of the condition under the title of "posterior basic (occlusive) meningitis, acquired hydrocephalus." These three writers were colleagues at the Hospital for Sick Children, Great Ormond Street, W C.

In 1888 Gee published an article of four pages "On the Coeliac Affection" beginning "There is a kind of chronic indigestion which is met with in persons of all ages yet is specially apt to affect children between one and five years old." At the time it attracted very little attention perhaps because, like most of his original papers, it appeared in the *St Bartholomew's Hospital Reports* and not in the medical periodicals with their much wider circulation. In 1903 W B Cheadle (1836–1910), his colleague at the Hospital for Sick Children, gave an account of cases under the name of "acholia" and ascribed them to "inhibition of the liver". Sir Byrom Bramwell (1847–1931) of Edinburgh in several papers between 1901 and 1915 described the condition as pancreatic infantilism, C A Herter (1865–1910) of New York "rediscovered" the disease in 1908 and started metabolic investigation of what he termed infantilism due to intestinal infection, Heubner (1843–1926) in the following year followed on the same lines, and the disease was sometimes called Gee-Herter and Herter-Heubner disease. The eponym "Gee's disease" appeared in 1926 in *The Manual of the International List of Causes of Death, as Adapted for Use in England and Wales Scotland and Northern Ireland* by the Registrar General, this tabular list contained a number of terms used by practitioners in signing death certi-

* Received for publication May 24, 1937

cates, and thus differs from *The Nomenclature of Diseases, Drawn up by a Joint Committee Appointed by the Royal College of Physicians of London* (1931) which gives very few synonyms and does not include "Gee's disease" The comprehensive article on this disease by Izod Bennett, Hunter, and Vaughan in 1932 was entitled "Idiopathic Steatorrhoea (Gee's Disease), A Nutritional Disturbance Associated with Tetany, Osteomalacia, and Anaemia" Since 1926 Thaysen of Copenhagen has written 10 papers arguing that the coeliac affection, non-tropical sprue, and tropical sprue should be grouped together under one designation "idiopathic steatorrhoea," and Mogensen of Copenhagen in 1937 suggested the eponym "Gee-Thaysen's disease" for those three conditions Henry Moore and his Dublin colleagues recommended that the coeliac disease of children should be called the "Gee-Herter disease," that idiopathic steatorrhoea of adults and adolescents of non-tropical countries should be known as the "Gee-Thaysen disease, and that the name sprue for the tropical disease should be retained" Years before his paper on the coeliac affection Gee's name became familiar in connection with a linctus composed of equal parts of compound tincture of opium, syrup of tolu, and oxymel of squill It was said that this prescription was not his, but that of a lady bountiful of a village, who had thus cured the obstinate cough of one of his hospital patients It became widely popular and in Smithfield, at the doors of the hospital which so freely supplied it to out-patients, "linctus tarts" were on sale It is interesting to recall his philosophical indifference to posthumous fame as merely meaning "the number of times after death the letters composing the man's name were put together in one order" (Legg)

Samuel Jones Gee was born on September 14, 1839, in London where his father, William Gee, was in business but was much interested in literature and frequented the British Museum His mother Lydia Sutton (1797-1888) was, like many mothers of great men, a remarkable woman His parents were somewhat puritanical Gee, the only one of their four offspring to survive infancy, was a delicate boy and never robust When eight years old he went to a private school in Enfield, a few miles from London, and from 1852 to 1854 he attended University College School Three years later he matriculated at the University of London, and as a medical student of University College Hospital came under the influence of Sir William Jenner (1815-98), whose example may in some degree have accounted for Gee's successful dogmatic teaching at the bedside In 1861 at the final examination for the degree of bachelor of medicine at the University of London he was bracketed with C Hilton Fagge (1838-83) for the gold medal and the University scholarship in medicine, in 1865 he proceeded to the M D degree and became a member, being elected five years later a fellow, of the Royal College of Physicians of London In the meanwhile he had become a member of the Royal College of Surgeons in 1863, and been appointed resident house surgeon to Richard Quain (1800-87) at University College Hospital in December 1862, earlier in that year he had been resident

house surgeon at the Hospital for Sick Children, Great Ormond Street. This hospital, the first solely for children in London, was founded in 1852 on the site of the mansion of that medical Maecenas, Richard Mead (1673–1754), largely as the result of the exertions of Charles West (1816–98), an



Samuel Gee

almost exact contemporary of Sir William Jenner, from 1848 to 1860 West lectured at St Bartholomew's Hospital Medical School on Midwifery, with which at that time diseases of children usually were nominally combined. It was not until 1904 that a special department for diseases of children was

established at St Bartholomew's Hospital, and was then placed under the care of Sir A. E. Garrod (1857-1936) and Dr H. Morley Fletcher, physicians to the Hospital and also on the staff of the Hospital for Sick Children and the East London (now Princess Elizabeth of York) Hospital for Children respectively. In Gee's time and for some years after, almost all the members of the staff of the Hospital for Sick Children were also attached to general Hospitals. Gee was appointed assistant physician in May 1865, physician in February 1875, and consulting physician in March 1885 to the Hospital for Sick Children. Like Thomas Addison and Hilton Fagge, particularly as regards dermatology, he was anxious to avoid the reputation of a specialist in any branch of medicine, and removed from the *Medical Directory* his title of consulting physician to the Hospital for Sick Children.

That Gee was house surgeon at University College Hospital and at the Hospital for Sick Children might now suggest that he inclined more to surgery than to internal medicine. But it is perhaps not generally realized that the post of house physician is more modern, at any rate in name, than that of house surgeon. At the Hospital for Sick Children the separate post of house physician was first established in December 1879. During the first half or more of the last century the work now done by house physicians was at most hospitals part of the duties of a resident medical officer, known as the apothecary, a title then in use for general practitioners. Thus at St Bartholomew's Hospital, London, Frederick Wood (1820-1906) was apothecary from 1847 to 1867 and performed the work later carried out by 14 qualified medical men, namely 10 house physicians, two junior assistant physicians, and two casualty physicians. In December 1867 four house physicians were created, and within a quarter of a century increased to ten. At Guy's Hospital the Stockers, father and son, were apothecaries, and the first resident house physician was appointed in 1868, a non-resident junior house physician being added in the following year, a house surgeon had been appointed in 1856. At the Radcliffe Infirmary, Oxford, there was a resident house-surgeon-apothecary until 1860 when a house physician was appointed, the last house-surgeon-apothecary but one there holding office for 12 years. At University College Hospital the name house physician at any rate was in use many years earlier, as is shown by the following information courteously supplied by the Secretary.

From its opening in 1834 the Hospital had an apothecary and a house surgeon. On December 7, 1841 the Medical Committee recommended that, as the duties of house-physician have always been performed by the apothecary, the titles as well as the duties of these offices be united, and after 1845 "house physician" often occurs in the Minutes. In 1851 on the recommendation of the Medical Committee the title apothecary was changed to resident medical officer, and in May 1880 that of "physician's assistant" to that of house physician.

In 1868 Gee was elected assistant physician to St Bartholomew's Hospital. It was then quite exceptional for the larger teaching hospitals in London to go outside their own school in order to fill vacancies on the permanent staff of the hospital. Indeed 20 years later a score of young would-be physicians were waiting about in the hope of becoming one of the eight on

the medical side of the staff During this period of probation the aspirants held minor teaching posts, such as demonstrators, in the medical school, or in connection with the hospital, such as medical registrars, on a salary so nominal as to be quite insufficient to keep body and soul together The competition was extremely severe and exacting, for it was not customary for the future consultants to engage in ordinary general or family practice, scholarships and grants for scientific research were then rarely available, and men without private means had to take pupils or undertake literary or other work to scrape together a living and to keep up appearances It was then and for years after a common complaint that many able men could not afford to become consultants The waiting time might be exceptionally tedious, especially when as very occasionally happened, several resignations and deaths occurred unexpectedly within a short time, and as a result the successors in office being comparatively young enjoyed an unusually long tenure of office, while their juniors had therefore to face a correspondingly increased period of probation At St Bartholomew's Hospital in the 'sixties of the last century the mortality among physicians was very high

William Baly (1814-61) in whose memory there is a gold medal for distinction in physiology at the Royal College of Physicians of London, was killed in a railway accident near Wimbledon, W S Kirkes (1823-64), distinguished for his work on embolism, the now forgotten hypothesis that chorea is due to miliary embolism in the corpora striata, and author of a textbook on physiology subsequently edited for many years by W D Halliburton (1861-1931), died from double pneumonia and pericarditis, a combination much more frequent then than now, Sir George Burrows (1801-81), afterwards president (1871-76) of the Royal College of Physicians of London, resigned in 1864, Henry Jeaffreson (1810-66) succumbed to typhus fever caught from a fatal case in a medical student under his care, G N Edwards (1830-68) died of renal disease, Robert Martin (1827-91) resigned in 1868 on account of a nervous breakdown when engaged to be married, this was a tragedy, for he soon recovered completely and returned to professional practice the next year in London, but a career of the brightest promise was irreparably wrecked, for "in London to step aside for a time is to be left behind" He was a charming white-haired gentleman with old-fashioned courtly manners, who often came to the post-mortem room or, as his generation called it, the dead house, and was an expert in the facial diagnosis of the cause of death He died of pneumonia, of which he had previously had an exceptional number of attacks, in 1869 F J Farre (1804-86) automatically ceased to be an active physician to the hospital on attaining the age-limit of 65 years

The way was thus opened for those waiting at St Bartholomew's Hospital, such as James Andrew (1829-97), Reginald Southey (1835-99), Sir William Church (1837-1928), and also for fresh blood, besides Gee, there were elected Sir Dyce Duckworth (1840-1928) in 1869 and Sir Lauder Brunton (1844-1916) in 1875, both Edinburgh graduates Wickham Legg (1843-1921), like Gee, a pupil of Sir W Jenner to whom, soon after Gee's election to St Bartholomew's Hospital, Sir James Paget said "Can't you send us another Gee?", was appointed to succeed Gee there as demonstrator of morbid anatomy in 1874, and as lecturer in that subject and assistant physician in 1878 He had qualified in 1867 and about this time was tutor to Prince Leopold (1853-84), the fourth and youngest son of Queen Victoria, this appointment was probably due to Sir William Jenner who from 1861 was the influential medical adviser of Her Majesty Prince Leopold was the subject of haemophilia on which Legg subsequently (1872) wrote

a treatise In 1883 he was selected by the president (Jenner) to deliver at the Royal College of Physicians of London the Bradshaw lecture founded in 1875 in memory of Dr W W Bradshaw of Oxford He chose "Cardiac Aneurysm" as his subject, and it may be noted that in 1889 Norman Moore (1847-1922) gave this lecture on "The Distribution and Duration of New Growths," and that Gee in 1892 followed in these footsteps of his juniors by lecturing on "The Signs of Acute Peritoneal Diseases" Legg's most considerable medical book was on "The Bile, Jaundice and Bilious Diseases" (1880) In 1887 he retired from St Bartholomew's Hospital and medicine to devote himself to liturgical subjects and bringing out numerous volumes for the Henry Bradshaw Society for editing rare liturgical texts, being Chairman of its Council from 1895 to 1915 Henry Bradshaw (1827-89), University Librarian, (1867-89) at Cambridge, and much interested in mediaeval liturgies inspired Moore, when a turbulent undergraduate at St Catherine's, with an interest in palaeography Gee, Legg, and Norman Moore who contributed 454 lives, mainly of medical men and Irish Saints to the first 63 volumes of the *Dictionary of National Biography* and others to its two supplements, formed a small group of colleagues, resembling the scholar-physicians in the time of Linacre (1460-1524), the founder and first president of the Royal College of Physicians of London Other like-minded contemporaries were W A Greenhill (1814-94), J F Payne (1840-910), and James Finlayson (1840-1906) of Glasgow, of these Norman Moore, the youngest and not the most profound, was probably the most successful in popularizing the history of medicine

At St Bartholomew's Hospital Gee was, for a short time in 1870, in charge of the skin department, established in 1867 This was in accordance with the rule then in force there that the assistant physicians and assistant surgeons should take charge of the special departments, and was in reality a compromising expression of the widespread dislike then felt by the leaders of the profession against specialism, a survival of the dictum that "a specialist is half a quack," ascribed to Sir Benjamin Brodie (1783-1862) who was president of the Royal Society, the Royal College of Surgeons of England, and the General Medical Council Gee found a more congenial occupation as demonstrator of morbid anatomy (1870-74), and lecturer on pathology from 1874 to 1878 when he became physician to the hospital and joint lecturer on medicine In obedience to the age limit of 65 years he became consulting physician in 1904

In 1901 he was appointed honorary physician to the Prince of Wales, afterwards King George V It has been suggested that his inability to yield to the weaknesses and foibles of mankind may have influenced the distribution of public honours as far as he was concerned, but probably, like Gallo, he "cared for none of these things" Indeed according to tradition, when asked by a most influential personage if he would like to be made a baronet, he replied that he would prefer a fur coat

With his clear and logical mind and after a most careful clinical examination of the patient Gee arrived at his diagnosis, which were very seldom wide of the mark, by an orderly process of exclusion and not by intuition. Osler spoke of him as combining the spirit of Hippocrates with the method of Sydenham. He was one of the best clinical teachers of his time in London, and his hospital rounds, made in the early afternoon, as is the custom in London, on three days in the week were always crowded, he naturally concentrated attention on the new cases, his opinion on nervous diseases being much quoted. Competition to be one of his clinical clerks for three months was keen, and to be his house physician, then resident for a year, W. H. R. Rivers (1864–1922) being the last under this arrangement, was a prize indeed. His house physicians, probably unconsciously, often adopted some of his peculiarities, such as turning back the lowest inch of their coat sleeves before examining a patient, this was a protection against parasitic invasion, and long before the time of white linen coats. The *Medical Notes* (1921) dedicated “to the Memory of My Teacher Samuel Gee” by Sir Thomas (now Lord) Horder, inevitably recall the collection of “Clinical Aphorisms from Dr. Gee’s Wards (1895–96)” which he published in 1897. In the early ‘eighties of the last century clinical medicine received comparatively little help from laboratory methods, clinical pathology being introduced at St. Bartholomew’s Hospital in the next decade, mainly by A. A. Kanthack (1863–98) the first whole-time teacher of pathology in the London medical schools. But I saw Gee sit down in one of his wards to stain sputum for tubercle bacilli soon after Koch described the method in 1882. As his colleague and friend Sir Thomas Barlow wrote, he was one of “the group of great Victorian physicians who held firmly the inseparable link between morbid anatomy and clinical medicine.”

At the Royal College of Physicians of London Gee was much in request, he held various offices and gave the following lectures. In 1871 the Goulstonian lectures on “The Heat of the Body”, this lectureship founded in 1632 by Theodore Goulston, M.D., F.R.C.P. is given to “one of the four youngest doctors of the College,” and it was further directed that a dead body should if possible be provided, a suggestion long ignored, the Lunleian lectures in 1899 on “The Causes and Forms of Bronchitis and the Nature of Pulmonary Emphysema and Asthma”, these lectures were endowed in 1581 by Richard Caldwell (1513–84), president of the College in 1570, and John, Baron Lumley (? 1534–1609), and was originally called in the annals of the College the Chirurgical Lectures, and the Bradshaw lecture which, as mentioned above, is of comparatively modern origin.

The Harveian Oration—the most honorable and perhaps the most difficult to discharge—Gee declined, perhaps more than once. It was founded in 1656 by William Harvey with a number of directions, some of which long ago fell into abeyance, for example, it was last delivered in Latin more than 70 years ago, and the complete commemoration by name of all the benefactors of the College is never attempted now. The reason suggested for

Gee's refusal was that being doubtful about the value of experiment in the natural sciences he felt that he could not obey Harvey's direction to exhort the fellows and members "to search and study out the secrets of nature by way of experiment" At the present day this attitude seems very strange, but Gee lived much in the past and preferred the old to modern ways It should, however, be mentioned that when Augustus Matthiessen (1831-70), lecturer on chemistry at St Bartholomew's Hospital Medical School, and C R A Wright discovered apomorphine in 1869 they handed it over for physiological investigation to Gee, who not only tried it on animals but was the first human being to be submitted to its action with the result that his initial scepticism about it being "a most powerful emetic and contrastimulant" was, as he fully admitted later, decisively demolished

Gee's personality was complex and therefore impressed people in different lights, he was thought by some to be shy and reserved, by others to be fastidious, he certainly was not a good "mixer" or of the "hail fellow well met" fraternity An unfavourable first impression was experienced by two of his life-long colleagues and friends

Francis Harris (1829-85) was elected assistant physician to the Hospital for Sick Children, Great Ormond Street, in 1859 and, in 1861 to St Bartholomew's Hospital, becoming full physician in 1868, he was thus Gee's senior colleague, the two men were very different, Harris being a Cambridge graduate of independent means who rather avoided private practice and was much devoted to field sports He had heard much about Gee, but without being attracted to him On one occasion when in poor health, he was advised by his friend Thomas Smith (1833-1909) to go away and get someone to take his out-patients, "Yes," said Harris, "but if there is one person I will not put on duty it is that beast Gee" He, however, was persuaded to do so, and eventually he and Gee became the greatest friends In his appreciative memoir Gee described a curious incident in connection with Harris's only published work—his thesis for the M D degree on "The Nature of the Substance Found in Amyloid Degeneration of the Various Organs of the Human Body" (1860) Not being accustomed to write for the press, Harris made little use of stops and in letters substituted dashes, in his thesis he followed his usual style, but when faced with the proofs was horrified by the numerous dashes which the printers had conscientiously copied

Howard Marsh (1839-1915), surgeon to St Bartholomew's Hospital and the Hospital for Sick Children, professor of surgery (1903-15) and Master (1907-15) of Downing College, Cambridge, described after Gee's death, the very frigid reception he received at their first meeting when he arrived, confessedly a day late, to succeed Gee as house surgeon at the Hospital for Sick Children, where later he and Sir Thomas Smith were Gee's colleagues and were instrumental in securing his election to the assistant-physiciancy at St Bartholomew's Hospital Marsh also mentioned Gee's outspoken criticism of men, how with his "eyes glowing with indignation and intense conviction" he would declare "the man is a scoundrel"

From Wickham Legg's *Recollections of Samuel Gee*, published in 1915, the following may be quoted, the first two *obiter dicta* having a somewhat Johnsonian flavour, "Sir, I have forgotten more anatomy than you ever knew", "Yes, Mill was an able fellow, but Bam was a dunderheaded Scotchman", his dismissal of the *Handbook of Therapeutics* (1869) by his contemporary Sydney Ringer (1835-1910) as "a book of little dodges", of the sudden death of Andrew Marvell the younger (1621-78) he said that it was not due to poison, but that he "was only murdered by his doctor who refused to give him the bark for a tertian ague" Many stories about him were current at St Bartholomew's Hospital, some apocryphal and even inherited from John Radcliffe (1658-1714) He was opposed to speculation, often quoting *hypotheses non fingo*, was profoundly critical and sceptical, and frequently changed his expressed opinion

He was prone to be pessimistic, thus in 1886 in a letter to Legg he sounded a despondent note "the struggle for life is so hard that those in the medical profession who are able to care for anything but making money are quickly becoming very few The learned physician is almost extinct And I am sorry for it, because the rank which the profession takes in the world depends chiefly upon the physicians" During the intervening 50 years the distribution of the relative spheres of influence has been much modified Of the modern Universities founded in the nineteenth century in England, including his own, that of London, he had a poor opinion When he had reached the three score years and ten of the psalmist he looked back without any satisfaction, care of his own health became something of a tyrant, and he concluded that life was but a sorry thing Describing himself as an "Old Whig" he had a contempt for politicians, did not read their speeches, and thought badly of this country's future

Wickham Legg who saw much of him heard him laugh heartily once only, Gee, however, had humour though generally dry and often so subtle that it escaped detection by the ordinary individual But there are exceptions to most rules, and Norman Moore, when laid up in Norfolk with an attack regarded as malarial, received from him the following lines

"I want to know, Moore, if you mean
To write a treatise on the spleen,
And if we find it does not plague you
To follow up with one on ague"

He hardly ever went to the theatre, painting, architecture, and music did not appeal to him in the least Norman Moore shared this lack of feeling for music, and could recognize one tune only, that of "God save the King," because every one then stood up Gee loved the birds and flowers of the country Like his teacher, Sir William Jenner, he strongly opposed the admission of women to the medical profession He was essentially a lonely soul, especially after the death of his wife and one of his two daughters Even as a younger man he preferred his own fireside to the

meetings of medical societies, at which his voice was little heard. But at the premier medical society in London, the Royal Medical and Chirurgical (expanded in 1907 into the Royal Society of Medicine), he sat on many committees and was honorary librarian (1887-99), being succeeded by Norman Moore. He certainly was not one of "the three Gs," three slightly junior contemporaries, so-called in the late seventies of the last century from their constant activities at medical societies in London, they were Sir W. R. Gowers, (1845-1915), Sir James Goodhart (1845-1916) and W. S. Greenfield (1846-1919), afterwards professor of pathology (1881-1912) at Edinburgh.

Extremely learned, Gee had read very widely from Hippocrates onwards and, though always pleased to discover that what was put forward as a new observation, had been anticipated by the Greeks he kept abreast of the modern German and French works on medicine. His favourite medical writers were Hippocrates, Sydenham and Heberden. His carefully trained memory seemed to retain all he read. His range of general literature was also extensive, especially of philosophy, he was attracted by the stoics, particularly Marcus Aurelius and Epictetus, and by the Cambridge Platonists, in 1872 he translated into English verse the hymn of Cleanthes (B. C. 300). Poetry, especially Wordsworth, appealed to him, and he was said to have known the whole of the "Prelude" and much of Pope's poems by heart, other favourite authors were Milton, George Herbert, Pascal, Montaigne, and Walter Scott. Matthew Arnold he spoke of as "the poet of despair." He was more in sympathy with the writers of the seventeenth and eighteenth centuries than with those of subsequent years. After his death it was said that he might have been a professor of English literature and equally well have occupied a chair of philosophy. With such encyclopaedic knowledge it is hardly surprising that he had a supreme contempt for any pretence of learning and hated a display of extensive reading. From the paucity of references in his published papers it would seem probable that he considered long lists of references as evidence of the author's vanity.

As a writer Gee began early and his concise style, which gave the maximum information in the fewest words possible, characterized his writing from the start, "thrift in words" being one of his mottoes. Sir John Russell Reynolds (1828-96), physician to University College Hospital enlisted with great success among the eminent contributors to his well-known *System of Medicine* in five volumes (1866-79) two young men from those under his eye at the hospital, Gee before he was thirty wrote in the first two volumes on chicken-pox, scarlet fever, and tuberculous meningitis, the last especially being an admirable study of the natural history of the disease. The other was Sir William R. Gowers who supplied classical articles on diseases of the blood-forming organs, being probably thus led to invent his haemocytometer (1877) and haemoglobinometer (1878), before his name became so predominantly associated with neurology—the branch of medicine which then especially attracted able young physicians.

Gee took much trouble in the choice of words, and preferred an English to any foreign word, thus "all of one mind" was better than "unanimous" and "hereafter" than "for the future". Legg thought that he took special interest in a man with dysentery who, when asked what he complained of, answered "Sir, the bloody flux". It was not unnatural that when asked in the closing years of the last century to write the article on pleurisy in Allbutt's *System of Medicine*, the successor of Russell Reynolds' *System*, he stipulated that no editorial changes should be made in what he had written. Later in conversation he expressed his dislike of "what is called getting up the literature" and this no doubt weighed with him in selecting T. J. (now Lord) Horder to revise the article for the second edition in 1909. But this expression of opinion was a few years before his death, and he had practised as well as preached the precept never to write on a subject until the literature had been thoroughly mastered. He contributed 46 papers to the *St. Bartholomew's Hospital Reports*, but wrote two books only. The first *Auscultation Percussion Together with Other Methods of Physical Examination of the Chest* appeared in 1870 and reached a fifth edition in 1907, the fourth edition being dedicated to the memory of Laennec. The text was largely composed as he walked to the hospital, when he would turn into a side street to jot down a sentence just constructed. From its logical form it has been compared to Euclid's propositions, and in 1901 he remarked "this book taught me more in the writing than it will teach anyone else in the reading". The other book *Medical Lectures and Aphorisms* appeared in 1902 and was dedicated to the memory of Sydenham. It passed into a fourth edition in 1915 when Wickham Legg added to it his "Recollections of Samuel Gee" with a signed and pleasing photograph. It contained 272 aphorisms of which 258 had been collected by J. T. Horder in 1897 who was his house physician and follower, they condensed a vast amount of practical medicine. The following may be quoted.

- No 59 "Pneumonia is not a local, but a universal disease, and the brunt of it may fall upon any part—lungs, endocardium membranes of the brain, intestines, kidneys"
- No 81 "Pericarditis is not so common now as formerly, a fact which must be attributed to the use of sodium salicylate in the treatment of rheumatic fever. Endocarditis, however, seems to be as common as ever"
- No 231 "Tache cérébrale is a sign of little or no value"
- No 257 "There is often a remarkable latency about diseases of old people. Phthisis particularly is often overlooked because of its supposed improbability"
- No 258 "As a rule people do not die 'of old age'. There is usually failure of a particular organ, and not of all together. Still, it is sometimes very difficult to say exactly from what an old person does die"

Gee's important paper on "The Clinical Enlargement of the Spleen in Hereditary Syphilis and Some Other Diseases in Children" was read on March 26, 1867 before the Royal Medical and Chirurgical Society. He showed that in the early stages of congenital syphilis the spleen was palpably enlarged in half the cases and reached a considerable size in a quarter of the cases, the mortality in the second category was very high, and the degree of splenomegaly was therefore an index of the severity of the infection. The paper, however, was not considered to be worthy of publication in the Society's *Transactions*, this was not a unique mistake in the somewhat erratic decisions of the Society's referees, for the same judgment was passed on the paper on the open-air treatment of tuberculosis in 1862 read by Henry MacCormac (1800-86), and on several papers between 1857 and 1860 on the recently described Addison's disease, though not by Addison who much resented this ruling. As Gee's paper was never published in full there was some misconception about its contents, and accordingly Sir Thomas Barlow at the great debate on visceral syphilis at the old Pathological Society of London in 1875 loyally asserted the value of Gee's conclusions. At one time Gee drew up a plan for a history of medicine, and he published a paper on "Sects in Medicine" (1889) and on Abraham Cowley (1903), but unfortunately he soon gave up the larger project.

Gee married on December 7, 1875 Sarah, daughter of Emanuel Cooper, a member of the Society of Friends, whom in the formal, old-world manner of speech, which in his young days had suggested that he too was a Quaker, he described to one of his colleagues as being "quite adequate". His best man was Robert Bridges (1844-1930) who was his pupil at St Bartholomew's, a colleague as assistant physician at the Hospital for Sick Children and poet Laureate in 1913. In his *Carmen elegiacum de Nosocomio Sti Bartholomaei Londinensi* (1877), dedicated to Patrick Black (1813-79), whose house physician he had been, Bridges summarized, in Ovidian verse, the characteristics of the staff, containing references to Gee such as *Tute, Gei, mihi quam dulce et habuisse magistrum*.

Gee died suddenly in an anginal attack on August 3, 1911, when with his surviving daughter at Keswick on the English Lakes, a necropsy, for which he had left instructions with his lawyer, showed extensive atheromatous change in the aorta and aortic valves. He left an estate of £34,879, not a large sum for a successful consulting physician.

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CASE REPORTS

ANEMIA AS THE CAUSE OF SEVERE CONGESTIVE HEART FAILURE REPORT OF A CASE

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THAT anemia can be the primary cause of organic heart disease is doubtful it can, however, give rise to quite abnormal subjective and clinical signs For such disturbances to arise it is necessary for the anemia to be severe It may be of the type characterized by a low level of the hemoglobin and a moderate reduction of the erythrocytes or of the type in which both factors are reduced Certain criteria are necessary before a diagnosis of heart disease attributable to anemia can be made, namely (1) presence of a marked anemia, and (2) disturbance of cardiac function

Herrick and Nuzum,¹ in 1918, first called attention to the association of pernicious anemia with angina pectoris They found four cases among 200 cases of angina pectoris Coombs,² in 1926, in a series of 36 cases of pernicious anemia found this combination in nine Cabot,³ in his book published in 1926 mentioned three cases of intense and typical angina and pernicious anemia without changes in the coronary arteries Herrick,⁴ in 1927, described three more instances, in two of which necropsy disclosed arteriosclerotic change of the coronary arteries He remarked on the rarity of the association

Willius and Giffin,⁵ in 1927, reported an incidence of 43 cases of angina in 1,560 cases of pernicious anemia These were cases in which the anemia was of long standing The angina had the same clinical features as the angina of coronary disease, but there were no changes detected in the heart and the electrocardiograms were normal

Reichel,⁶ in 1929, reported a series of 114 instances of pernicious anemia with angina pectoris present in three Gwyn,⁷ in 1932 in a consideration of angina pectoris and anemia stated his opinion that the coronary artery must have undergone some pathologic change to produce the syndrome The absence of angina pectoris in most cases of severe anemia was suggested as being attributable to the fact that the entire heart has degenerated and hence the ventricular balance is not upset Case reports on this subject by many authors 7, 8, 9 10, 11, 12, 13 14, 15, 16, 17, 18 have appeared

Gunewardene,¹⁹ of the Indian Medical Service reported in 1933 on the frequency of heart failure in ankylostomiasis In these cases severe anemia and marked cardiac dilatation accompanied by signs of congestive failure were often present On treatment and cure of the infection the heart returned to normal size and the murmurs disappeared Smith,²⁰ in 1933, made an electrocardiographic study of the heart in 15 cases of severe anemia The blood pressure in seven of these was normal In none were characteristic alterations of any sort found, in any phase of the electrocardiographic deflections

* Received for publication December 1, 1936

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Pickering and Wayne,²¹ in 1933, reported on 25 cases of anemia. Eight of these patients complained of substernal pain with or without exertion. In six cases pain did not continue after the anemia had been cured. In two it persisted. The occurrence was not restricted to any particular type of anemia. The tolerance to exercise seemed to improve with the elevation of hemoglobin, but pain could still be produced with greater exertion. In four severely anemic patients the same exercise no longer produced pain or tightness in the thorax when the level of hemoglobin in the blood was 50 per cent.

Elliott,²² in 1934, reported a case of anemia, caused by repeated severe uncontrollable epistaxis, with severe angina in the presence of healthy coronary arteries and aorta. The heart at necropsy weighed about 601 gm. There was no clinical evidence of hypertension. The cardiac hypertrophy was explained on the basis of the chronic anemia. The stress of exertion together with the acute loss of blood was felt to be sufficient to precipitate myocardial ischemia with resultant angina pectoris. The electrocardiogram showed alterations in the R-T segment.

Ball²³ reported a case in which changes in the heart were demonstrated by roentgenology in the presence of severe anemia. This was a case of severe menorrhagia from fibroids in which there were definite symptoms of myocardial failure with enlargement of the heart and murmurs. After surgical removal of the uterus the murmurs disappeared and the roentgenogram revealed reduction in the size of the heart on return of the blood to normal.

In severe anemia certain changes in function of the cardiovascular system do occur. In the early stage the pulse rate increases and then an elevation of the blood pressure appears with a relative decrease in the pulse pressure. This changes later into a true cardiac and vascular insufficiency. A recent report by Grunberg²⁴ based on 111 cases, 49 of which were cases of pernicious anemia and 62 of secondary anemia, demonstrated this change. Changes in the size of the heart were also noted with enlargement to the right and left as the anemia progressed.

Changes in the cardiovascular mechanism during anemia are entirely the result of an attempt at compensation. Fahr and Ronzone²⁵ studied the circulatory compensation for deficient oxygen capacity of the blood in severe anemia and found that there was an increase in the minute volume output of the blood in addition to a lowered viscosity of blood and that the skin capillaries were contracted to half normal size in an effort to increase the blood flow through the vital organs. One can conceive of this attempted compensation going to the point where partial or complete failure of the heart ensues.

CASE REPORT

A white man, a printer aged 76 years, was admitted to the hospital June 12, 1935, complaining of severe dyspnea on exertion and orthopnea of three months' duration. A family history of diabetes and of numerous gastrointestinal diseases was obtained. He had been married for 30 years and had had no children. His past history was essentially negative except for a history of indigestion for 15 years associated with vomiting of blood on two occasions and black stools on one occasion. All three of these episodes were 15, 13 and 11 years before admission respectively. For years he had taken soda to relieve his epigastric pain which usually came on one hour after eating. He had never had distress at night. For the last year he had taken soda

almost every day because of epigastric pain. He had been watching his stools carefully but had not noticed gross blood or tarry stools.

Three months before admission the patient had begun to notice dyspnea on walking up a slight incline to his office. He had no associated pain in the thorax. The dyspnea seemed to get worse each day and although he did not stop walking, when he arrived at his office he was gasping for breath and it was necessary for him to sit down and rest. He consulted his physician five weeks before admission and was told he was jaundiced and had a severe anemia. A potent preparation of liver was prescribed which the patient continued to take for five weeks. No improvement resulted. His dyspnea progressed so that it appeared on the slightest exertion. It was impossible for him to lie down and sleep, so he sat in a chair most of the time. Prior to onset of his illness he had lost about 10 pounds in weight, but in the last three months his weight had increased gradually and swelling of the entire body had occurred.

Examination on admission to the hospital revealed an extremely pale old man with moderate swelling of the face. His weight was 206 pounds. The blood pressure taken while he was at rest in bed was 154 mm of mercury systolic and 74 diastolic. The pulse rate was 100 beats per minute and was regular. There was a slight icteric tinge to the sclerae and a suggestion of jaundice of the skin. His voice was quite hoarse and there was an irritating, non-productive cough. The pupils which were small and irregular reacted sluggishly to light. The teeth were all absent. The thyroid gland could not be palpated. The thorax and arms were edematous so that pressure produced deep pitting. No gross pleural fluid could be detected but coarse rales were heard through the lower portion of both lungs. The heart was percussed slightly to the left of the midsternal line. Its tones were distant, regular and no murmurs were present. The abdomen contained a large quantity of free fluid. The abdominal wall showed marked pitting edema. Although the liver was not palpable there was definite tenderness in the right upper quadrant of the abdomen. The scrotum and peris were moderately edematous and the legs revealed marked pitting edema. The rectal examination was essentially negative.

The laboratory studies revealed the number of erythrocytes to be 1,800,000 per cubic millimeter of blood. The value for hemoglobin was 35 per cent. The total leukocyte and the differential counts gave normal results. The urine had a specific gravity of 1.020, was alkaline in reaction and contained a trace of albumin. The phenolsulphonphthalein test was 45 per cent in two hours. The value for non-protein nitrogen was 28 mg and for urea nitrogen, 17.7 mg. The value for serum protein was 6.4 gm, for cholesterol, 96 mg, for blood sugar, 120 mg, for serum bilirubin 2.6 mg and for blood chloride, 531 mg per 100 cc. The Hinton reaction of the blood was negative. The venous pressure was 22 cm. The stools were found to contain blood. Analysis of gastric content revealed a total acid of 54 and a free acid of 36.

Because of the marked edema and since the kidney function was apparently normal, measures to induce diuresis were instituted. The patient was given ammonium chloride, the intake of fluid was restricted and 14 cc of salyrgan were administered in divided doses in 15 days. Marked diuresis resulted, the patient losing 60 pounds. His general condition improved as the edema lessened and when his weight reached 146 pounds, he said that he felt fine and the edema and orthopnea had disappeared.

Investigation was instituted immediately to determine the source of the blood in the stools which had persisted in spite of a meat-free diet. The patient's condition was so improved that roentgenologic studies of the stomach were carried out and these revealed a persistent niche at the junction of the first and second portions of the duodenum with a rather marked narrowing at this point.

A diagnosis of duodenal ulcer with chronic bleeding and severe secondary anemia was made and dietary treatment and administration of large doses of iron were begun. At the time the patient was dismissed from the hospital, or 25 days after admission,

the erythrocyte count was 3,080,000 and the value for hemoglobin 44 per cent. One and a half months later the erythrocyte count was 5,260,000 and the value for hemoglobin, 94 per cent. At that time also the patient's weight was 151 pounds. He felt perfectly well and was back at work. He did not have the slightest evidence of dyspnea on walking, slept flat in bed and had no evidence of gastric distress. At present, one and a half years after his dismissal from the hospital, he is in good health and is working every day.

COMMENT

On admission to the hospital this patient presented all the features of severe cardiac decompensation. His condition responded to administration of diuretics in the usual way for primary heart disease with failure. On alleviation of the secondary anemia the patient was able to return to his activities and his cardiac symptoms disappeared. This patient had the usual amount of arteriosclerosis for patients of his age, but there was no associated hypertensive or valvular disease and no history to suggest myocardial infarction. That the anemia was the precipitating factor in the decompensation of the heart seems certain and is further borne out by the course of the disease. No digitalis has been used by the patient since he was dismissed from the hospital.

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THE DIAGNOSIS OF SOLITARY LIVER ABSCESS BY MEANS OF THOROTRAST HEPATOSPLENOGRAPHY

Report of a Case *

By WALLACE M YATER, M D, F A C P, and JOHN R CAVANAGH, M D,
Washington, D C

DURING the past five and one-half years we have employed Thorotrast for the purpose of demonstrating lesions of the liver and spleen in several hundred patients. This method of roentgenographic diagnosis was developed mainly by Oka¹ and Radt² about 1929. It consists in the intravenous injection of 50 to 75 c c (for adults) of a stabilized colloidal solution of thorium dioxide manufactured under the name of Thorotrast,† following which roentgenograms of the abdomen are made. The thorium dioxide is rapidly engulfed by the reticulo-endothelial cells of the body, and because it is radiopaque it is possible to demonstrate the size, shape and structure of the liver and spleen, which contain these cells in greatest concentration. Cirrhosis of the liver and neoplasms are particularly well shown. Although thorium dioxide is somewhat radio-active and remains for years in the body we have not observed serious immediate or remote ill effects from its use. Yater, Otell and Hussey³ have reviewed their first 200 patients examined over a period of five years and have failed to note harmful results. They describe the technic and the information that can be derived from the study of hepatosplenograms. Their first patient has recently returned for a checkup five and one-half years after the injection of 60 c c of Thorotrast. Although the roentgenogram shows shadows of the liver and spleen almost as dense as originally, she is in the best of health, in spite of the fact that the diagnosis of chronic lymphatic leukemia was made by competent clinicians six years ago and roentgen-ray treatment employed therefor.

* Received for publication February 15, 1937

From the Georgetown University School of Medicine

† Manufactured by the Heyden Chemical Company

The opportunity to demonstrate liver abscess by means of hepatosplenography does not present itself often and we feel justified in reporting a case. Reeves and Apple⁴ used Thorotrast for this purpose successfully in a case of amebiasis reported in 1933.

CASE REPORT

Clinical Course A white barber, aged 38 years, entered Georgetown University Hospital on July 24, 1936. Prior to May 10, 1936 he had been well since childhood, when he had had measles, mumps, pertussis and chicken-pox. On May 10, 1936 he had developed a severe attack of pain in the right upper quadrant of the abdomen which radiated to the right axilla. After a few days he had returned to work in spite of continued but less severe pain. Six weeks before admission the pain became worse and fever was first noted. The pain was practically continuous from then on and the fever persisted. The pain was described as sharp and stabbing, starting about 8 cm. to the right of the umbilicus and radiating to the right costal margin. There was also a dull, constant ache in the right lumbar region. For three weeks before admission he had vomited at intervals. A loss of 40 pounds had resulted. On the day before admission a chill had occurred. There had been no bowel disturbance.

The patient appeared to be seriously ill. There was no jaundice. The temperature was 101° F, the pulse rate 100, and the respiratory rate 22 per minute. There were numerous carious teeth, the tongue was dry, and the tonsils were hypertrophied and slightly inflamed. The heart and lungs appeared normal and the diaphragm moved normally bilaterally. The abdomen was flat and symmetrical. On deep palpation there was marked tenderness over the lower portion of the right lobe of the liver, which could be felt about 6 cm. below the right costal margin and seemed to have a rounded edge. The hemoglobin was 56 per cent, the red blood cells numbered 3,180,000 and the white blood cells 26,050 per cu. mm. of blood, with 82 per cent polymorphonuclear neutrophils. Other laboratory studies including urinalysis, van den Bergh reaction, bromsulphthalein test of liver function, Wassermann and Kahn tests of the blood, and repeated stool examinations were normal or negative.

During the first two and a half weeks in the hospital the temperature was very irregular and ranged from 98° F to 103° F, being elevated practically every day. The condition became progressively worse, and a bronchitis aggravated the pain. Abscess of the liver was suspected early and it was decided to make hepatosplenograms. On July 27, 28 and 29, by intravenous administration 25 c.c. of Thorotrast were given, and on July 30 a roentgen-ray film was made of the abdomen. The appearance of the film, interpreted in conjunction with the clinical course, was definitely that of a large solitary abscess of the right lobe of the liver. Further roentgen-ray films were made at intervals after operation.

On August 10, 1936, Dr. William C. Gwynn opened the abdomen and found the right lobe of the liver to be enlarged with a rounded edge, and a rounded mass about the size of a medium-sized orange projected from its under surface. The omentum and parietal peritoneum were sutured to the anterior surface and edge of the liver adjacent to the mass, and a gauze packing was placed in the pocket thus formed. Two days later the incision was re-opened and an aspirating trocar and cannula inserted through the isolated area of liver into the mass. About 150 c.c. of thick reddish brown pus were aspirated, after which a large rubber drainage tube was placed in the abscess cavity and the area again packed with gauze. Pus continued to drain in gradually diminishing amount. Amebae or other organisms were not found in the pus, but a course of injections of emetine hydrochloride was given. On the tenth day after operation the tube was removed and the wound slowly healed. The irregular fever continued for three weeks after operation, when the temperature be-

came normal. The patient was discharged as cured on the fortieth day after operation.

On March 10, 1937 the patient was re-admitted to the hospital. He had remained well until one week before, when he became feverish and weak. During this week he had had several chills, and tenderness had developed in the upper right quadrant of the abdomen. Examination revealed slight enlargement of the liver, tenderness near McBurney's point, and dry rales in both lungs. The temperature on admission was 104.6° F, the pulse rate was 120 and the respiratory rate 20 per minute.



FIG 1 Pre-operative hepatosplenogram, showing enlarged right lobe of liver with large area of lessened density in lower portion, the demarcation not being clear cut.

The blood pressure was 85 systolic and 58 diastolic. The urinalysis was normal. The hemoglobin was 57 per cent, erythrocytes numbered 3,600,000 and leukocytes 14,800 per cubic mm of blood, with 84 per cent polymorphonuclear neutrophils. A roentgenogram of the chest showed an area of opacity in the middle of the right lung field, which was thought to indicate interlobar pleurisy. A barium study of the colon showed a constant area of narrowing of the transverse colon, which was thought to be due to an adhesion from the old operative scar. A hepatosplenogram was made, this did not throw any light on the present illness. Several stool examinations were negative for amebae. A blood culture was negative. The Craig test for amebiasis gave questionable results. The temperature became normal after

ten days The hemoglobin and erythrocyte count gradually rose to normal, while the leukocyte count rose to 17,000 The course of injections of emetine hydrochloride was repeated but not until after the temperature had been normal for several days The patient left the hospital after four weeks, apparently well The exact cause of the liver abscess or of the second illness was not determined

Description of Hepatosplenograms The first films showed the right lobe of the liver to be moderately enlarged downward (figure 1) There was normal hepatic opacity in the upper three-fifths of the liver shadow, but the lower rounded portion



FIG 2 Hepatosplenogram made two weeks after operation for solitary abscess, showing abscess cavity about half its original size

was relatively non-opaque The upper rounded edge of this non-opaque area was not sharp but was rather "fuzzy," characteristic of an abscess without a well formed wall The left lobe of the liver was not enlarged, and the spleen was of normal size Films made two days before operation were quite similar A hepatosplenogram made two weeks after operation showed the abscess cavity to be about half its original size (figure 2) One month after operation the right lobe of the liver was practically normal in size, and the abscess cavity was about one-fourth its original size Two months after operation there was a small mottled area of somewhat less opacity than the main mass of liver in the lower edge of the right lobe (figure 3) Apparently the

abscess cavity had contracted and become filled in with reparative tissue. The reproductions of these hepatosplenograms show far less detail than the films themselves. The hepatosplenogram made in March 1937 showed no appreciable change from the previous one.



FIG 3 Hepatosplenogram made two months after operation, showing healed area in lower portion of right lobe of liver

COMMENT

The conditions that must be differentiated from solitary abscess of the liver in hepatosplenograms are neoplasm and cyst. Neoplasms, especially metastatic carcinoma, are usually multiple. They appear as round areas of lessened opacity with a clear cut edge and often a halo of condensed liver tissue about them. Solitary tumors of the liver are rare but have a sharper outline than abscess. The same is true of echinococcus cyst. While the outline of an abscess is irregularly circular, it is not sharp but "fuzzy" and blends with the adjacent liver parenchyma. It has a homogeneous appearance in its central portion as does a neoplasm, since pus does not contain reticulo-endothelial cells, at least

none capable of removing foreign bodies from the blood stream. The roentgen appearance should be pathognomonic when the clinical history is considered in conjunction with it. Hepatosplenography is merely a laboratory method of diagnosis and should be employed by the clinician and roentgenologist with the clinical picture in mind, although often a correct diagnosis of hepatic lesions can be made from a study of the films alone.

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EDITORIAL

BENIGN LYMPHOCYTIC CHORIO-MENINGITIS

In 1925 Wallgren¹ collected and described under the term "acute aseptic meningitis" a group of cases of meningitis which began abruptly and ran a benign course, which showed a lymphocytosis in the cerebrospinal fluid from which no bacteria could be isolated by smear or culture, and in which the recognized diseases capable of causing this symptom complex could be excluded. Since this publication many similar cases have been reported both in America and in Europe, and the condition is evidently not uncommon.

The clinical picture has varied considerably. The onset may be preceded by symptoms of an acute respiratory infection, or of "influenza." More often it is abrupt, with severe headache, fever, drowsiness, photophobia, vomiting and stiffness of the neck. In the mildest cases headache may be the principal complaint, and after an illness of two or three days, the symptoms may subside and permanent recovery ensue. More often the illness lasts from one to several weeks, but recovery eventually occurs without sequelae. In other cases the symptoms are more severe. There may be delirium, dizziness, marked drowsiness or excitability, restlessness and apprehension. Anorexia and constipation are usually marked. Transient pareses or even paralyses, usually of the cranial nerves, have been described, but there are no outspoken paralyses, as in poliomyelitis. There may be respiratory disturbances. Kernig's sign is often positive. Reflex disturbances are common, either exaggeration, diminution, or inequality of the deep reflexes. There is often slight swelling of the optic discs. Viets and Warren² have reported one case that died after convulsive seizures.

The cerebrospinal fluid has been found under increased pressure. The fluid is colorless, clear or slightly turbid. The cells are always increased, usually from 200 to 2000 or more above the norm, and over 90 per cent are lymphocytes. The lymphocytosis persists for several weeks in convalescence. In the severer cases the globulin is increased and the sugar and chlorides somewhat diminished. Cultures are sterile and tubercle bacilli are not found. The colloidal gold test may show a meningitis type of curve.

In the case of Viets and Warren there was a marked lymphocytic infiltration of the meninges, which extended deep into the brain substance along the vessels. There were areas of degeneration and gliosis, and in places the nerve cells showed inclusion bodies.

Recent investigations have shown that in a limited number of these cases the disease is due to a filtrable virus. This was first isolated by Armstrong

¹ WALLGREN, A. Une nouvelle maladie infectieuse du système nerveux central? *Acta Paediat*, 1925, iv, 158.

² VIETS, H. R., and WARREN, S. Acute lymphocytic meningitis, Jr. *Am. Med. Assoc.*, 1937, cviii, 357.

and Lillie in 1933³ from the brain of a monkey, the sixth in an inoculation series, the first of which had been inoculated with the brain emulsion of a human case supposedly of encephalitis of the St Louis type. In 1935 Scott and Rivers⁴ isolated a virus, later found to be identical, from the cerebrospinal fluid of two human cases of the disease, by intracerebral inoculation into mice. Traub⁵ also obtained the same virus from a colony of mice which had been naturally or accidentally infected.

Intracerebral inoculation into mice of infected cerebrospinal fluid or virus suspensions causes an encephalitis in most of the animals. The symptoms appear after five to six days and consist chiefly of tremors, clonic convulsions, and tonic spasm of the hind legs. The virus is present in the brain, but also in the blood and other organs. At necropsy the animals show a lymphocytic infiltration of the meninges and choroid plexus and a virus bronchopneumonia. Those which survive are immune to reinoculation.

Monkeys can be infected by intracerebral inoculation, and the disease may spread spontaneously among them.

Guinea pigs are highly susceptible, both to intracerebral and subcutaneous inoculation. After seven or eight days they show fever, which may be the only symptom, loss of weight and signs of general illness. The distribution of the virus and the lesions are like those in mice. Guinea pigs which survive become immune, and their serum will neutralize the virus and prevent the infection of other mice or guinea pigs. The serum of human cases has also acquired protective power, but this develops only after six to ten weeks.

Because of the characteristic pathological lesion the disease caused by the virus is commonly called benign (or acute) lymphocytic chorio-meningitis. Clinically it must be differentiated especially from tuberculous meningitis, from poliomyelitis, from epidemic encephalitis, and from the encephalitis that occasionally occurs as a sequel of various other virus diseases such as mumps and vaccinia. A positive diagnosis can be made by demonstrating the virus in the spinal fluid at the onset of the disease by inoculation into mice or guinea pigs. It may also be made by demonstrating protective power in the serum late in convalescence. One of these procedures is necessary since many cases showing this clinical picture fail to show the virus in the cerebrospinal fluid and do not develop protective power, and presumably are due to some other etiological agent.

The wide distribution of the disease is shown by the fact that Armstrong demonstrated protective power in the serum of six individuals from widely separated sections of this country. Furthermore Findlay, Alcock and

³ ARMSTRONG, C., and LILLIE, R. D. Experimental lymphocytic chorio-meningitis of monkeys and mice produced by virus encountered in studies of the 1933 St. Louis encephalitis epidemic, *Pub. Health Rep.*, 1934, **XLIX**, 959.

⁴ SCOTT, T. F. McN., and RIVERS, T. M. Meningitis in man caused by a filterable virus, *Jr. Exper. Med.*, 1936, **LXIII**, 397.

⁵ TRAUB, E. Filterable virus recovered from white mice, *Science*, 1935, **LXXXI**, 298.

Stern⁶ recovered the same virus from cases of human infection and from mice in England. It is not certain whether man or the mouse constitutes the primary reservoir of infection, but it is believed to be man. Further study will probably show that the disease is more common than the number of reported cases would suggest. Recognition is important, particularly from the standpoint of prognosis, although the occurrence of severe and even fatal cases must be recognized.

⁶ FINDLAY, G. M., ALCOCK, N. S., and STERN, R. G. Virus aetiology of one form of lymphocytic meningitis, *Lancet*, 1936, i, 930.

REVIEWS

Body Water By JOHN P. PETERS, M.D. viii plus 405 pages, 16 × 23 cm Charles C. Thomas, Springfield, Illinois 1935 Price, \$4.00

In spite of the extensive literature covered in "Body Water," this monograph can hardly be regarded as a general review of the water balance. No mention is made, for example, of the total water content of the body or of the distribution of fluid in various organs. Dr. Peters has quite frankly limited himself to those phases of this broad subject in which he and his co-workers have been particularly interested. The book might best be described as a critical analysis of some of the basic problems pertaining to the exchange of fluid in man. The author has clearly made a determined effort to see just how far the known facts can be explained by physico-chemical laws, and failing to find a satisfactory explanation on this basis, he stretches neither facts nor laws for the sake of reaching definite conclusions. Unfortunately, the result of this searching attitude seems to be a book in which the reader finds it difficult to extricate the facts from the discussions.

"Body Water" begins with a detailed discussion of the "chemical forces involved in exchange of fluid and solutes." One-third of the book is then devoted to the internal fluid exchange, following which there are two chapters on "Water of oxidation and the losses of water and solute through the skin and respiratory passages" and "Alimentary exchanges." The remaining third of the book is concerned entirely with the kidney.

Dr. Peters does not hesitate to deal harshly with existing theories. For example, he launches a vigorous campaign against the views of Drinker and Field on the mechanism of lymph formation. Contrary to the opinion of these authors, he also contends that the amount of protein in tissue fluid is small as compared to that present in lymph. In reviewing the chemical data on cerebrospinal fluid, Dr. Peters finds inadequate support for the hypothesis that this fluid is a simple ultrafiltrate of serum. Recent evidence discrediting the once popular theory of "bound water" is also cited.

The first chapter on osmotic pressure is in certain respects misleading. Osmotic pressure is simply an expression of the difference in diffusion pressure of the solvent in different parts of the system, and not due to a tendency of the solutes to expand as Dr. Peters seems to imply by the following statement: "The solutes which exert pressure in a solution are restrained by the boundaries of the fluid system in which they may be dissolved. Changes of the volume of the system cannot be effected by direct expansion of the solutes as they are in gases but only by the addition of solvents."

The emphasis here is upon the solute whereas in reality the only part that the solute plays in the phenomenon is that of "diluting" the solvent.

The discursive nature of many sections of "Body Water" makes it rather difficult reading for those chiefly interested in general information. This characteristic of the book, however, is perhaps not due so much to the author's method of presentation as to the complexities of a subject in which many of the fundamental facts are still lacking. A more didactic treatment would in many instances be unjustified and serve only to give the erroneous impression that general agreement existed on questions which are far from settled.

M I G

A Mind Restored By ELSA KRAUCH 242 pages, 14.5 × 21 cm G. P. Putnam's Sons, New York 1937 Price, \$2.50

This book, bearing an introduction by William Seabrook, author of "Asylum" and of various travel tales, is another account of the experiences of a man suffering mental illness which required hospitalization. The tale describes the development of

a common type of depression which gradually progressed to the point that this man was unable to care for his own affairs, lost his business, went through a "rest home," a small, private sanatorium of the type which is unhappily not uncommon and finally had himself voluntarily admitted to a state hospital. After a period of months in the state hospital he made a social recovery and in the course of the next two years feels that he has recovered completely. Certainly he is again apparently a useful, self-supporting member of society and one who has learned a great deal from the experiences he lived through. Most of the book is devoted to his experiences in and reactions to the state hospital.

During the past several years there have been a number of such tales intended for general reading, designed to allay some of the fears which exist about mental disease and about conditions which are popularly supposed to exist in our institutions. A great many physicians find these books of the better type useful in demonstrating to their patients that other people suffer the same experiences and in giving the patient's family some allegedly inside information. This is one of the best of such books. It gives a fairly satisfactory, objective account of life in a state hospital. It is not Pollyannish, neither is it bitter. It will probably be a good book for selected depressive patients, particularly middle-aged groups and for families to read. It is one of the few books of this type which can be recommended for this purpose.

H M M

Allergic Diseases Their Diagnosis and Treatment By RAY M. BALYEA, M.A., M.D., F.A.C.P., Assisted by RALPH BOWEN, B.A., M.D., F.A.C.P. Fourth Edition. xv plus 516 pages. F. A. Davis Company, Philadelphia. 1936. Price, \$6.00.

In the preface to the first edition of this work, the author states that it is written primarily to teach patients "concerning the possible causes of their trouble so that they may acquaint themselves more thoroughly with the animal and plant life with which they are surrounded, as products from one or both of them frequently cause their attacks." In the preface to the present edition, he revises this, stating that it has not been written for those doing special work in allergy, but for the general practitioner.

In attempting to estimate the usefulness of the volume, its content seems to be too voluminous and detailed for a patients' manual, and, at least in part, too elementary to be very useful to the physician. Thus, there seems to be no very good reason for the inclusion in a patients' handbook, of detailed directions for the intratracheal administration of iodized oil, nor should the patient be familiar with the technic of collection, staining, and examination of nasal secretions. Though an effort has been made to keep the terminology simple enough to be understood by the intelligent layman, technical expressions, without adequate explanation, are frequently used. The physician who expects much help in the treatment of patients, will probably be disappointed in the complete lack of detail as to methods of hyposensitization by hypodermic administration of atopens. The omission of a discussion of constitutional treatment reactions, and the author's statement that they do not occur (p. 225) are surprising.

On the whole, however, this volume is easy to read, interesting, and, at times, valuable. The section on botany is very helpful, well illustrated, and contains a number of pollen maps. Directions to patients for the elimination of offending substances should be useful.

I N C

Diseases of the Nose and Throat By C J IMPERATORI and H J BURMAN 16 X 23 cm, 723 pages J B Lippincott Company, Philadelphia 1935

This new work on the diseases of the nose and throat is one that can be used by both senior medical students and practitioners alike. The volume consists of 52 chapters and 480 illustrations, covering 723 pages. It begins by giving a detailed description of office equipment and arrangement. This is followed by an outline of history taking and methods of examining the patient.

A review of the anatomy and physiology is presented, followed by discussion of the various affections of the nose and throat. One is accustomed to having etiology and pathology presented early in the discussion of a disease, but the authors have preferred to present first the symptoms, then the diagnosis, treatment (medical and surgical), pathology, complications, etiology, and prognosis in the order named.

The descriptions of operative technic are very clear and well illustrated.

A rather lengthy description of the diseases that can be diagnosed and treated with the aid of the bronchoscope and esophagoscope is included. A chapter is devoted to physical therapy methods in diseases of the nose and throat. Allergic manifestations in the upper respiratory tract are adequately discussed.

The style is very simple, it is one of the easiest of books to read. The type is large and the topics are arranged in somewhat the form of an outline. There are not a lot of unnecessary details to wade through, but at the same time nothing essential is omitted.

T R O'R

Reports on Chronic Rheumatic Diseases By THE BRITISH COMMITTEE ON CHRONIC RHEUMATIC DISEASES, Edited by C W BUCKLEY, M D, F R C P 159 pages, 17 X 25 cm Number one 1936 The Macmillan Co, New York Price, \$4 00

The stated purpose of this report by the British Committee on Chronic Rheumatic Diseases is to stimulate interest and research in the causes and treatment of rheumatic conditions and to develop more coordination of information and activities not only in Great Britain, but throughout the world.

The book is divided into three parts. The first includes a foreword, a description of the Committee organization, and a report of the Subcommittee on Nomenclature. A series of seven original articles on various phases and types of arthritis forms the second part, and four articles of review type constitute the third part. An extensive world-wide bibliography of articles written during 1936 completes the book, the arrangement of this section is by country, which gives one a better opportunity of comparing the activities of each nation.

The report of the Nomenclature Subcommittee is very interesting and is very detailed. It not only suggests a workable classification but explains its merits. The section on Clinical Criteria offers ample material for discussion and comparison of facts between the arthritis of known etiology and that of unknown. A careful and complete collection of all facts and features of each type is presented in apposing columns.

The original articles present material of much interest and value. The section called Critical Commentaries offers a review of the important international literature of the year and in general summarizes the feature articles from many countries and from different branches of medicine and surgery.

The report as a whole makes very interesting and instructive reading and tends to carry out its basic idea, namely to stimulate international coordination of thought and action in so important a disease. It may well be studied by student, practitioner and specialist.

A F V

COLLEGE NEWS NOTES

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Dr John Kenneth Deegan (Fellow), Ithaca, N Y —1 reprint,
Dr Elliott B Edie (Fellow), Uniontown, Pa —1 reprint,
Dr Harold G F Edwards (Fellow), Shreveport, La —6 reprints,
Dr John T Farrell, Jr (Fellow), Philadelphia, Pa —3 reprints,
Dr A Allen Goldbloom (Fellow), New York, N Y —2 reprints,
Dr George Alexander Gray (Fellow), San Jose, Calif —1 reprint,
Dr Jacob Gutman (Fellow), Brooklyn, N Y —1 copy, eleventh supplement to "Modern Drug Encyclopedia",
Dr C L Harrell (Fellow), Norfolk, Va —2 reprints,
Dr James W Hunter, Jr (Fellow), Norfolk, Va —2 reprints,
Dr Henry J John (Fellow), Cleveland, Ohio —11 reprints,
Dr Joseph E Knighton (Fellow), Shreveport, La —3 reprints,
Dr L Winfield Kohn (Fellow), New York, N Y —3 reprints,
Dr Maurice Kovnat (Fellow), Staten Island, N Y —1 reprint,
Dr Charles A LaMont (Fellow), Canton, Ohio —1 reprint,
Dr H Beckett Lang (Fellow), Brentwood, N Y —2 reprints,
Dr George M Levitas (Fellow), Westwood, N J —1 reprint,
Dr Philip B Matz (Fellow), Washington, D C —5 reprints,
Dr James L McCartney (Fellow), Catskill, N Y —1 reprint,
Capt K C Melhorn (Fellow), M C, U S N —1 reprint,
Dr M A Mortensen (Fellow), Battle Creek, Mich —1 reprint,
Dr Henry Monroe Moses (Fellow), Brooklyn, N Y —1 reprint,
Dr Frederick W Mulsow (Fellow), Cedar Rapids, Iowa —3 reprints,

Dr Hilton S Read (Fellow), Atlantic City, N J—1 reprint,
 Dr Rafael Rodriguez-Molina (Fellow), San Juan P R—3 reprints,
 Dr William J Ryan (Fellow), Pomona, N Y—1 reprint,
 Dr F Jannev Smith (Fellow), Detroit, Mich—1 reprint,
 Dr Norman Strauss (Fellow), New York, N Y—1 reprint,
 Dr William Henry Wash (Fellow), Chicago, Ill—4 reprints,
 Dr Morris Deitchman (Associate), Youngstown, Ohio—1 reprint,
 Dr William Freeman (Associate), Worcester, Mass—1 reprint,
 Dr Barnett Greenhouse (Associate), New Haven, Conn—1 reprint,
 Dr George B Lake (Associate), Waukegan, Ill—3 reprints
 Dr William G Leaman, Jr (Associate), Philadelphia Pa—3 reprints,
 Dr Aleksei A Leonidoff (Associate) Poughkeepsie, N Y—1 reprint,
 Dr David J Sandweiss (Associate) Detroit, Mich—3 reprints,
 Dr Albert Weinstein (Associate), Nashville, Tenn—1 reprint

Dr Carl H Gellenthien (Fellow), Valmora, N M, presented a lecture on "The Diagnosis and Differential Diagnosis of Pulmonary Tuberculosis" before the Diagnostic Clinic and Fifteenth Annual Assembly of Twin Lakes District Medical Society at Burns' Alhambra Pavilion, Twin Lakes, Rockwell City, on June 17

Dr B S Pollak (Fellow) Secaucus, N J, sailed on July 31 for Lisbon, Portugal, to attend the bi-annual Conference of the International Union Against Tuberculosis, which will be held at Lisbon September 5 to 9

Dr Edward E Cornwall (Fellow), Brooklyn, N Y, read a paper on "Diet and Longevity" before the American Therapeutic Society at its annual meeting held at Atlantic City, June 4

The following Fellows of the College were selected as speakers in connection with the tenth annual Graduate Fortnight, presented by the New York Academy of Medicine, from November 1 to 12

Dr George Baehr, New York, N Y, "The Pathology of Nephritis",
 Dr Robert F Loeb, New York, N Y, "Clinical Aspects of Nephritis",
 Dr Herman O Mosenthal, New York, N Y, "Clinical Aspects of Hypertension, Including Malignant Hypertension"

Dr Homer Davis (Fellow), Genoa, Nebr, has been elected President-Elect of the Nebraska State Medical Association

At the recent annual meeting of the North Carolina State Tuberculosis Association, held in Southern Pines, Dr Paul A Yoder (Fellow), Winston-Salem, N C, was elected President of the Association

Dr Roland A Davison (Fellow), Tucson, Ariz, has been appointed Medical Director of the Desert Sanatorium, succeeding Dr Louis B Baldwin (Fellow), Tucson, Ariz

Dr Alphonse McMahon (Fellow), St Louis, Mo, was elected President of the American Therapeutic Society at its annual meeting held in Atlantic City in June

Dr F M Pottenger (Fellow, Regent, and Past President) presided as President at the meeting of the Association for the Study of Internal Secretions, held at Chalfonte-Haddon Hall, Atlantic City, June 7 and 8, 1937 His presidential address was on the subject of "Early History of the Association for the Study of Internal Secretions" Dr Pottenger had previously served as President of the Association during the term 1935-1936, and was Secretary of the Association during the years 1917 to 1935

Dr Pottenger also gave an address on the evening of June 4 at the meeting of the American Therapeutic Society in Atlantic City His subject was "The Clinical Versus the Public Health Point of View in the Treatment of Tuberculosis"

Dr George W McCoy (Fellow), former director of the National Institute of Health, Washington, D C, has been assigned by the U S Public Health Service to make a study of leprosy in continental United States and the island possessions

Dr John E Gordon (Fellow), field director of the International Health Division of the Rockefeller Foundation, New York, has been appointed professor of preventive medicine and epidemiology at Harvard University Medical School

Dr Austen Fox Riggs (Fellow and Life member) received an honorary degree of Doctor of Science from Williams College, Williamstown, on June 21, 1937

Dr Edgar M Dunstan (Fellow) has resigned as Medical Director of Baylor Hospital to become Superintendent of the Dallas City County Hospital System

Dr Fred M Mevner (Fellow) Peoria, Illinois, represented the National Tuberculosis Association of the United States at the meeting of the British National Association for the Prevention of Tuberculosis at Bristol, England, July 1, 2, 3 He addressed the conference on "Nutrition and Environment in Open Air Schools" and also on "Dispensary Methods"

OBITUARIES

DR MUNFORD SMITH

Dr Munford Smith (Fellow) of Los Angeles, California died of cerebral thrombosis June 28, 1937 aboard the Motor Ship Canada bound for Panama. Dr Smith had left with Mrs Smith for the ocean trip as part of a convalescence from a recent period of ill health.

Dr Smith was born December 3, 1892, in Pittsburgh, Pa. He had his early education there and at Bucknell College. He received his medical degree from the University of Maryland in 1919. That same year he became associated with the Barlow Sanatorium which association he held at the time of his death. He was Medical Director of the Sanatorium for the past ten years. Dr Smith was active in many organizations. He was a member of the Los Angeles County, California State and American Medical Associations, the California Tuberculosis Association, a director of the National Tuberculosis Association and President of the American Sanatorium Association. He was an able and popular man, active and interested in his work with many friends both in and out of the profession who greatly miss him and his activities.

EGERTON L. CRISPIN, M.D., F.A.C.P.

DR C. L. SHERRILL

Dr Cote Long Sherrill (Fellow), of Statesville, North Carolina, the son of Walter and Anna Long Sherrill, was born September 4, 1887, in Texas. He received his academic education at Wake Forest College, N. C., and graduated in medicine at the North Carolina Medical College in Charlotte in 1914. He spent his internship at the Stetson Hospital, Philadelphia, and pursued post-graduate studies in several New York Hospitals, the Mayo Clinic, and various other clinics of the country.

Entering the U. S. Army in November, 1917, he was commissioned a captain, promoted to his majority in May, 1918, and sailed for France in August of that year. He was discharged July 19, 1919, as a lieutenant colonel, later entering the Medical Reserve Corps as a full colonel, which commission he held at the time of his death. He was very active in Legion affairs, was local Post Commander for one term, and held various executive offices with the state department of the Legion. He was elected National Commander of the Wildcat Division in 1936.

He was chief of the medical department of the H. F. Long Hospital, Statesville, N. C., at the time of his death, June 24, 1937, of coronary occlusion. His medical societies embraced his local and state medical societies, the American Medical Association, and he was made a Fellow of the American College of Physicians in 1931. For several years he had served as a member of the Postgraduate Committee of the N. C. State Medical Society,

and at the last meeting of this society he was also made Chairman of this Committee as well as Chairman of the Section on Medicine

In 1917 he married Miss Mary McLam, and leaves three living children in addition to his widow. He was a member of the Methodist Church, and was considered a leading spirit in the affairs of his community. His hobby was fishing. While not given to writing or publication, he was a faithful attendant of the medical societies to which he belonged, an earnest student of medicine, a hard worker, and a fine gentleman who will be missed by all who knew him.

C. H. COCKE, M.D., F.A.C.P.,
Governor for N. C.

DR. WILLIAM WALLACE BEHLOW

Dr. William Wallace Behlow (Fellow), Lieutenant Commander, Medical Corps, United States Navy, retired, died April 29, 1937, at the Palo Alto Hospital, Palo Alto, California.

Dr. Behlow was born in San Francisco April 8, 1886. He was a graduate of Leland Stanford University, receiving the degree of A.B. in 1907. In 1912 he received the degree of M.D. at Harvard University, following which he interned at the Boston City Hospital. Following his internship he returned to California where he practiced his specialty, internal medicine, and served on the Faculty of the Medical School of the University of California.

On the declaration of war in 1917, Dr. Behlow patriotically gave up his private practice of medicine and enrolled in the United States Naval Reserve in the provisional grade of Assistant Surgeon. He reported for active duty at the Navy Yard, Mare Island, California on May 26, 1917. Following this he took the professional examination for entrance into the Medical Corps of the Navy and he was commissioned an Assistant Surgeon in the regular service dating July 19, 1917. In April, 1918, Dr. Behlow reported on the destroyer *U. S. S. Taylor* for duty at sea, and in 1919 he was transferred to the battleship *U. S. S. Idaho* as junior medical officer with the present Surgeon General of the Navy. This was followed by duty at the Recruiting Station, Salt Lake City, Utah, and an assignment with the Second Base Force, U. S. Marines, San Diego, which was followed by a tour of duty with the Bureau of Medicine and Surgery in the Personnel section. His next assignment was to the hospital ship *U. S. S. Relief*. From this duty he went to the United States Naval Hospital, Brooklyn, New York, where he was later hospitalized and finally placed on the retired list. Following retirement he reestablished his residence in San Francisco, California.

Dr. Behlow was commissioned a Passed Assistant Surgeon with the rank of Lieutenant, U. S. Navy, on June 6, 1920. He was commissioned Surgeon with the rank of Lieutenant Commander, U. S. Navy, on June 4, 1925 and he was placed on the retired list on December 1, 1931.

Dr Behlow was a very high type of medical officer professionally and personally, and was regarded as an outstanding internist among his colleagues. He was noted particularly as a specialist on contagious diseases. He was unmarried.

P S ROSSITER, M D , F A C P ,
Governor for United States Navy

DR PETER JURJENS POTHUISJE

Dr Peter Jurjens Pothuisje (Fellow), of Denver, Colorado, died June 4, 1937

Dr Pothuisje was born in Holland on February 27, 1866 and was naturalized at Seattle, Washington, about 1887. He received his pre-medical training at DePauw University and his medical training at the University of Ohio, graduating in 1893. At various times he pursued postgraduate work in Chicago and New York City.

Dr Pothuisje was Consultant in Internal Medicine to St Joseph's Hospital since 1910, to St Luke's Hospital since 1922, to St Anthony Hospital since 1906, and to Beth Israel Hospital since 1923. He was on the active service of the Denver General Hospital. He was a member of the Medical Society of the City and County of Denver, the Colorado State Medical Society, and the American Medical Association, and had been a Fellow of the American College of Physicians since 1924. During the World War, he served with rank of First Lieutenant U S A.

Dr Pothuisje is survived by his wife, Lois Renette Tabor Pothuisje, and by two daughters, Lois, the wife of Dr Ivan W Philpott, of Denver, and Lucille, the wife of Mr Lawrence Stubbs, of Wichita, Kansas.

Dr Pothuisje was an able internist, devoting special attention to gastroenterology. He was a beloved family physician and those who knew him have suffered a great loss.

GERALD B WEBB, M D , F A C P ,
Governor for Colorado

DR VAUGHAN LE ROY SPRENKEL

Dr Vaughan Le Roy Sprenkel (Associate), Allentown, Pennsylvania, died June 18, 1937, at the Jefferson Hospital, Philadelphia, as a result of a cerebral accident terminating a chronic state of purpura hemorrhagica.

Vaughan Sprenkel was born in Perkasio, Pa, in 1906. He attended the Public Schools of Perkasio, York and Allentown and completed his pre-medical education at Muhlenberg College, Allentown. He graduated, with honors, from the Jefferson Medical College, Philadelphia, in 1931. Dr Sprenkel's internship was served at the Sacred Heart Hospital, Allentown, and in June 1932 he married and began his professional practice in Allentown.

Tragedy entered his life when his young bride died, in 1933, as the result of a complication after childbirth but, like the brave man he ever proved to be, Dr Sprenkel sublimated his grief and sorrow by attempting to help others

To write the obituary of a physician who lived but 31 years and whose professional life was, as a consequence of its brevity, very largely preparation for a future of work must give one pause

Those intimately associated with Vaughan Sprenkel are aware that from boyhood he was a practical idealist and, as he matured, he selected the profession of medicine as an agency of altruistic and unselfish service to others

After receiving his medical degree and completing his internship Dr Sprenkel planned and executed an admirable course of postgraduate instruction

His routine visits to Philadelphia hospitals kept him informed concerning the scientific work of a medical center and his enthusiasm, industry and earnestness brought him to the attention of those deeply interested in the progress and future of honorary scientific and medical associations

Dr Sprenkel became an Associate Fellow of the College in 1935. He was the youngest member of the International Association of Medical Museums and was, also, one of the youngest men to be selected for the honor of membership in the American Therapeutic Society. Dr Sprenkel's brief professional career was successful in the highest and best sense of that much abused term

He had learned in his student and interne days that the profession of Medicine must ever remain an Art, with a sound basis of Science and from the day he entered practice he was wisely far more interested in his patients than in the disease they were suffering from. Dr Sprenkel was admired and loved by those who knew him best and the medical profession and our College has suffered a serious loss in the too early passing of this talented young physician

E J BEARDSLEY, M D , F A C P ,
Governor for Eastern Pennsylvania

MINUTES OF THE BOARD OF GOVERNORS

St Louis, Mo

April 19, 1937

The first meeting of the Board of Governors of the American College of Physicians, held in connection with the Twenty-first Annual Session, St Louis, Mo, was called to order at 5 05 p m, April 19, 1937, at the Jefferson Hotel, with Dr Charles H Cocke, Chairman, presiding and the following Governors, or their representatives, present, and with Mr E R Loveland acting as secretary of the meeting Dr Fred W Wilkerson, Dr H P Mills (representing Dr W Warner Watkins), Dr Turner Z Cason, Dr Glenville Giddings, Dr James G Carr, Dr C W Dowden, Dr E H Drake (representing Dr Edwin W Gehring), Dr Henry M Thomas, Jr, Dr G W F Rembert, Dr Louis H Fligman, Dr R W Mendelson (representing Dr LeRoy S Peters), Dr J R Scott (representing Dr Walter W Palmer), Dr A B Brower, Dr T Homer Coffen, Dr Charles T Stone, Dr Louis Warfield (representing Dr Rock Sleyster), Dr James F Churchill, Dr G B Gilbert (representing Dr Gerald B Webb), Dr Wallace M Yater, Dr Samuel E Munson, Dr Robert M Moore, Dr Thomas Tallman Holt, Dr William B Breed, Dr Maurice C Howard (representing Dr Adolph Sachs), Dr Allen A Jones, Dr Leander A Riely, Dr E L Bortz (representing Dr E J G Beardsley), Dr Clement R Jones (representing Dr E Bosworth McCready), Dr J Owsley Manier, Dr Louis E Viko, Dr W E Ogden (representing Dr Jabez H Elhott), Dr Oliver C Melson, Dr Clarence K Canelo (representing Dr Ernest H Falconer), Dr Joseph E Knighton, Dr Henry R Carstens, Dr Edward L Tuohy, Dr A Comingo Griffith, Dr H W N Bennett (representing Dr Robert B Kerr), Dr Clarence L Andrews, Dr Charles H Cocke, Dr C F Gornly (representing Dr Alexander M Burgess), Dr Kenneth M Lynch, Dr J Morrison Hutcheson, Dr Charles E Watts, Dr Walter E Vest, Dr D Sclater Lewis, Dr Perceval S Rossiter, Dr Thomas Parran and Dr Edgar V Allen (Adviser to Dr E L Tuohy)

Chairman Cocke declared those attending the meeting as alternate Governors were automatically seated, if their credentials had been presented to the Executive Secretary, or to him

Abstracted Minutes of the preceding meetings of the Board of Governors at the 1936 Session were read, and, upon resolution, were approved

At this point, Chairman Cocke recognized the President of the American College of Physicians, Dr Ernest B Bradley, who addressed the Board He especially stressed the efficient aid the Governors had given to the College, and especially to the Committee on Credentials during the past year

Chairman Cocke then reported upon the deliberations of the Board of Regents at its earlier meeting He referred particularly to two amendments, one to the Constitution and one to the By-Laws, which had been considered by the Board of Regents at their December, 1936, meeting and subsequently published in the "Annals of Internal Medicine" These amendments related to limitations in the membership outside of Internal Medicine and to new standards of admission He said that after more mature thought and study, the judgment of the Board had been that the amendments should not be presented at the present time, on which there would be a further report at the General Business Meeting of the College

Chairman Cocke also referred to the matter of the Governors being the guests of the Regents during the past two or three years at the opening of the Annual Sessions, and expressed the hope that the Board of Governors might do something a little more concrete than just extend formal thanks

On motion by Dr Allen A Jones, seconded and unanimously carried, it was

RESOLVED, that the Board of Governors extend to the Board of Regents an invitation to Dinner at the opening of the 1938 Session

Secretary Loveland was called upon to present communications, whereupon he reported that he had received many letters from Governors who were unable to be present, several appointing others to act in their stead

Chairman Cocke read to the Governors the list of candidates for Associateship and Fellowship who had been elected by the Board of Regents on April 18, and reported that their names would be posted on the Bulletin Board, where every one could consult the list

Chairman Cocke then presented the list of Associates who were subject to being dropped for failure to qualify for Fellowship in the five-year period The list had been reported to all the Governors concerned by the Executive Secretary, but each Governor was now given an opportunity to make any supplementary report before definite action had been taken by the Board of Regents

Dr C W Dowden requested information as to how an Associate so dropped might later qualify for Fellowship The Executive Secretary reported that there had been but two cases that had come up as precedents In one case the Associate had not qualified for Fellowship because of serious illness He was later permitted to be proposed directly for Fellowship and not required to serve another five-year term as an Associate The other case also had some extenuating circumstances connected with it, with the result that the candidate was considered directly for Fellowship as a special case However, there must be adequate reason for such special consideration

Chairman Cocke then presented the list of members who were subject to being dropped for two years' delinquency This list also had been previously circulated among the Governors, so that every one was informed Every one on the delinquent list had been advised on many occasions of his delinquency, and the Executive Secretary now felt there was no further action that could be taken, other than to proceed with the provisions of the By-Laws Various members on the list were discussed, and no changes were made

Dr Cocke then reported upon the eighteen additions to Life Members since the last meeting, making a total of seventy-eight He also reported upon the acquisition of the new College Headquarters, describing its architecture, location, facilities, etc, and invited the members of the Board to visit the headquarters whenever they are in Philadelphia

Dr Wilkerson, Governor for Alabama, proposed that the meetings of the College be so arranged as not to conflict with the meetings of the Alabama State Medical Association There was general discussion of the time of the meetings, but it was pointed out that it is impossible to arrange the meetings of the College without some State society in some part of the country later selecting the same time Chairman Cocke, however, said that the program committee took every possible step to avoid conflicts

Dr E L Tuohy, Governor for Minnesota, inquired as to how much credit is given to the character of histories and autopsies presented by candidates Chairman Cocke replied that all histories and autopsies presented by candidates are examined by the Committee on Credentials to determine if they give evidence of careful preparation, proper history taking, proper laboratory studies, and correlation and discus-

sion of findings and diagnosis. He pointed out that the Committee on Credentials not infrequently returns histories which they feel have been delegated to secretaries or internes. Dr Cocke further pointed out that candidates are also judged from other standards, such as the presentation of publications, theses or proof of certification by one of the national certifying boards.

Dr Tuohy then recommended that the American College of Physicians should resort also to some sort of a report from the hospitals in which candidates are doing their work. This would act as an indirect means of inducing candidates to be more diligent and to more carefully observe the rules and regulations of the institutions. These sorts of inquiries, in addition to the presentation of histories, theses, etc., would give a further line-up on the character and qualifications of the candidates.

Chairman Cocke agreed to convey this suggestion to the Committee on Credentials, and suggested to Dr Tuohy that he also discuss the matter with the Chairman of this Committee.

In further discussion of the matter, it was pointed out that the superintendent of some hospitals is a nurse whereupon the suggestion was made that these inquiries should be sent to the Chief of Staff.

Dr Robert M Moore, Governor for Indiana, made a further suggestion that candidates who have recently changed from a large center to a small center should be given a period of time to become established before being considered for membership. The small city presents some obstacles to the continued restriction of practice to Internal Medicine, and some delay in accepting such candidates may afford a period of observation to determine whether they will be eligible in the new location.

Chairman Cocke then requested all members of the Board of Governors to join the Convocation procession on the evening of April 21.

Adjournment

Attest E R LOVELAND,
Executive Secretary

MINUTES OF THE BOARD OF GOVERNORS

St Louis, Mo

April 21, 1937

The second meeting of the Board of Governors of the American College of Physicians, held in connection with the Twenty-first Annual Session, St Louis, Mo, was called to order at 12 50 p m, April 21 1937, at the Jefferson Hotel, with Dr Charles H Cocke, Chairman, presiding, and Mr Loveland acting as secretary. The roll call disclosed the following Governors, or their representatives, present: Dr H P Mills (representing Dr W Warner Watkins), Dr Turner Z Cason, Dr Glenville Giddings, Dr James G Carr, Dr C W Dowden, Dr E H Drake (representing Dr Edwin W Gehring), Dr G W F Rembert, Dr Louis H Flugman, Dr R W Mendelson (representing Dr LeRoy S Peters), Dr A B Brower, Dr T Homer Coffen, Dr Charles T Stone, Dr Louis Warfield (representing Dr Rock Sleyster), Dr James F Churchill, Dr Wallace M Yater, Dr Samuel E Munson, Dr Robert M Moore, Dr Thomas Tallman Holt, Dr William B Breed, Dr Maurice C Howard (representing Dr Adolph Sachs), Dr Allen A Jones, Dr Leander A Riely, Dr E L Bortz (representing Dr E J G Beardsley), Dr J Owsley Manier, Dr Louis E Viko, Dr W E Ogden (representing Dr Jabez H Elliott), Dr Oliver C Melson, Dr Clarence K Canelo (representing Dr Ernest H Falconer), Dr Joseph E

Knighton, Dr Henry R Carstens, Dr E L Tuohy, Dr A Comingo Griffith, Dr Clarence L Andrews, Dr Charles H Cocke Dr C F Gornly (representing Dr Alexander M Burgess), Dr J Morrison Hutcheson, Dr Charles E Watts, Dr Walter E Vest and Dr D Slater Lewis

Chairman Cocke thanked the alternate Governors for attending the Session and the meetings of the Board

Upon motion by Dr C W Dowden, seconded by Dr A B Brower, and regularly carried, it was

RESOLVED, that the reading of the Minutes of the preceding meeting of the Board of Governors be dispensed with

Chairman Cocke reported on the preceding meetings of the Board of Regents, mentioning particularly the following items

(1) The Board of Regents has determined to appoint a Committee on Exhibits and Advertising to make a thorough survey, and to report back upon standards for raising the character and type of exhibits at the Annual Sessions and the type and character of advertising accepted in the ANNALS OF INTERNAL MEDICINE,

(2) The Board of Regents has appointed a Committee to formulate plans for a Revolving Fund to be available for Associates of the College to pursue postgraduate work to adequately qualify themselves for the examinations of the American Board of Internal Medicine,

(3) The Board of Regents has appointed a Committee on Postgraduate Education to organize courses of from two to four weeks either preceding or immediately following the Annual Sessions of the College these courses to be available to Fellows and Associates of the College at minimum cost These postgraduate courses will be organized in connection with the next Annual Session of the College They will cover every branch of Internal Medicine In view of the fact that the College always holds its Annual Sessions in large medical centers exceptional postgraduate facilities will be available,

(4) The Board of Regents has appointed a Consulting Committee to work with the Executive Secretary in connection with the publication of the 1937 Directory of the College, this Committee to have power in determining how Fellows and Associates shall be listed, and to designate what specialties and sub-specialties shall be recognized in the Directory

In the discussion that followed it appeared to be the consensus of opinion that the Board of Governors favor listing Fellows and Associates in the same section of the Directory, and not in separate sections as heretofore A suggestion was made that under the geographical index, the names of Fellows should be listed first and the names of Associates should be listed immediately thereunder

On motion by Dr C W Dowden seconded by Dr O C Melson, it was

RESOLVED, that the above recommendation be communicated to the Committee on the Directory and to the Board of Regents

On motion by Dr C W Dowden, seconded by Dr O C Melson, and regularly carried, it was

RESOLVED, that a transcript of the discussion by the Board of Governors be transmitted to the Consulting Committee on the Directory (Full discussion is recorded verbatim in the Executive Secretary's office)

There was a general discussion of the postgraduate courses to be offered by the College, it being pointed out that the courses are distinctly for members of the College, that the courses would be furnished at a very much lower cost than they are available elsewhere Dr Vest suggested that the courses should be made available also to candidates for membership

Upon motion by Dr Holt, seconded by Dr Dowden, it was

RESOLVED, that the Board of Governors recommend to the Board of Regents that the postgraduate courses extend over a period of not less than two weeks and possibly up to a period of a month

The Executive Secretary distributed mimeographed copies of the financial reports for the year 1936, and then proceeded to answer questions and explain various details related thereto

Chairman Cocke called for a discussion among the Board of Governors of the subject "allied specialties" as it now appears in the Constitution and By-Laws of the College

Dr Griffith moved and Dr Melson seconded the following motion

RESOLVED, that the Board of Governors recommend to the Board of Regents the retention in the Constitution and By-Laws of the words "and allied specialties"

The motion was opened for discussion, Dr Cocke explaining that "allied specialties" refer to pediatrics, neurology, psychiatry, pathology, tuberculosis, pharmacology, dermatology, bacteriology, roentgenology and public health. He explained further that the retention of these specialties within the scope of the College would continue to make available to the College the results of the investigations by men in these specialties

Dr Cason, Governor for Florida, expressed the opinion that the allied specialties should be eliminated. For example, he pointed out that the pediatricians have their own society and their own certifying board, the same being true in some of the other allied specialties, such as roentgenology. He felt that practitioners of the allied specialties would attend the meetings of the College less and less

Dr Breed, Governor for Massachusetts, expressed the opposite opinion, saying that he felt it would be suicidal for the College to restrict itself to the term Internal Medicine. The allied specialties should be retained within the By-Laws, and the gastroenterologists, dermatologists, etc., should be discouraged from setting up their own certifying boards

Dr Munson, Governor for southern Illinois, expressed the opinion that those engaged in the allied specialties who are interested in the College should be retained, and that programs of clinics should be provided to retain their interests

Dr Carr, Governor for northern Illinois, expressed the opinion that in keeping the pre-clinical men in the College, the College not only is showing respect for them, but will eventually obtain the help of men who are doing the most work along investigative lines. He said it would be a tragedy to eliminate from his part of Illinois those who are working continually and doing investigative work. The professors of physiology, bacteriology and pathology, and their associates in the medical schools of Chicago, are a decided asset to an institution like the College. They are called upon whenever a study of the fundamentals of medicine are desired. Such men had given him valuable help in the conduct of the Chicago program of the College

Dr Andrews, Governor for New Jersey, pointed out that whether the College membership is restricted to Internal Medicine or not, the program committee is free to invite surgeons, pathologists, or any others, to give papers and to participate in the clinics. He expressed the opinion that he favored the time when members of the College could say that the American College of Physicians is restricted to Internal Medicine

Dr Dowden, Governor for Kentucky, pointed out that the difficulty in the proposition under discussion had arisen in an effort to properly define the word "internist". In further discussion, he distinctly favored the retention of the "allied specialties" within the College. Many of those practicing allied specialties need a higher knowledge of Internal Medicine than many others who practice Internal Medicine exclusively

Chairman Cocke pointed out that certification by the American Board of Internal Medicine should not be construed as being synonymous with Fellowship in the American College of Physicians. Membership in the College may mean much more than mere certification, because other considerations would enter into the matter of Fellowship than mere certification.

After further discussion of the definition of membership in the American College of Physicians, the question was put to a vote and the resolution unanimously adopted.

Adjournment

Attest E R LOVILAND,
Executive Secretary

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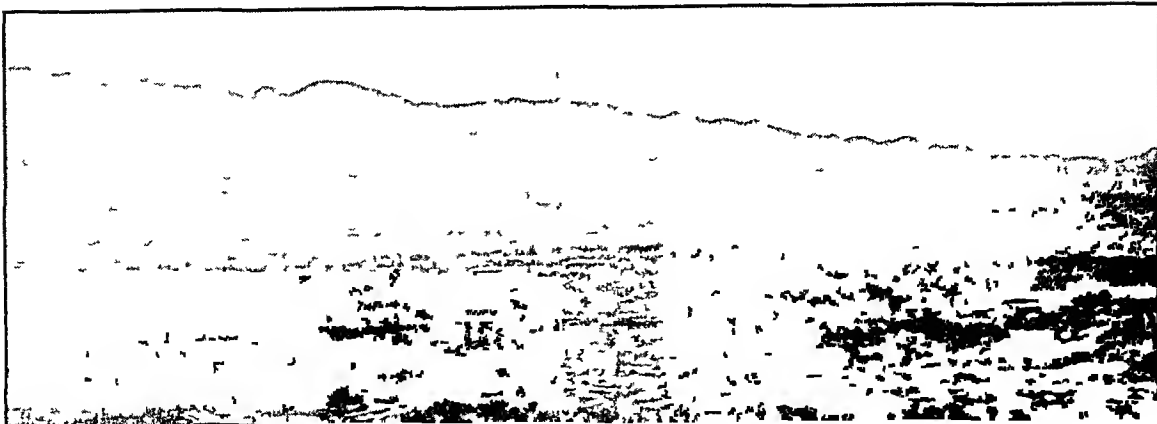
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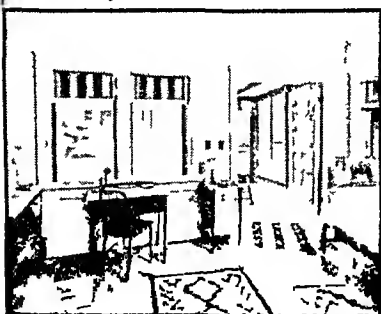
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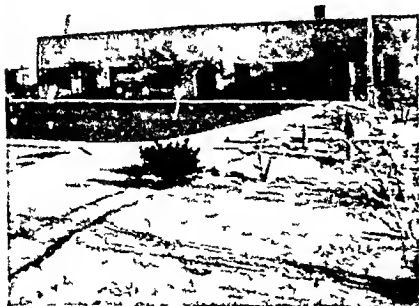


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Place of Publication—Prince and Lemon Sts, Lancaster, Pa

Editorial Office—University Hospital,
Baltimore, Md

Executive Office—4200 Pine Street,
Philadelphia, Pa

THE ANNALS OF INTERNAL MEDICINE is published by the American College of Physicians. The contents consist of contributions in the field of internal medicine, editorials, book reviews, and a section devoted to the affairs of the College.

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ANNALS OF INTERNAL MEDICINE

PUBLISHED BY

The American College of Physicians

VOL 11 (O S, Vol XVI) SEPTEMBER, 1937

NUMBER 3

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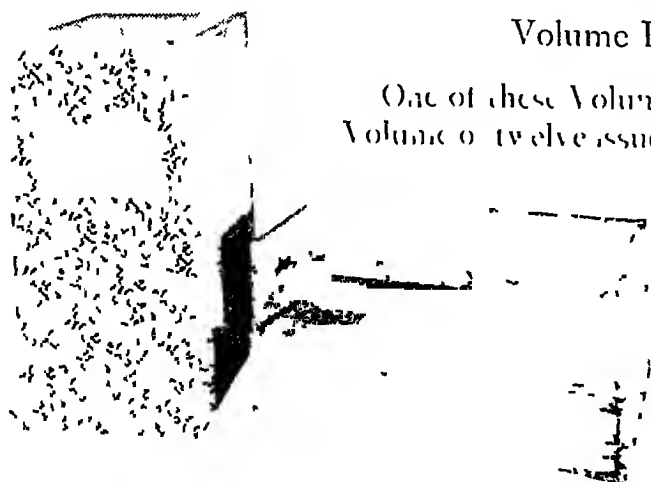
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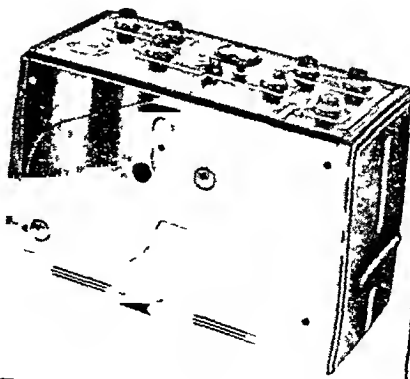
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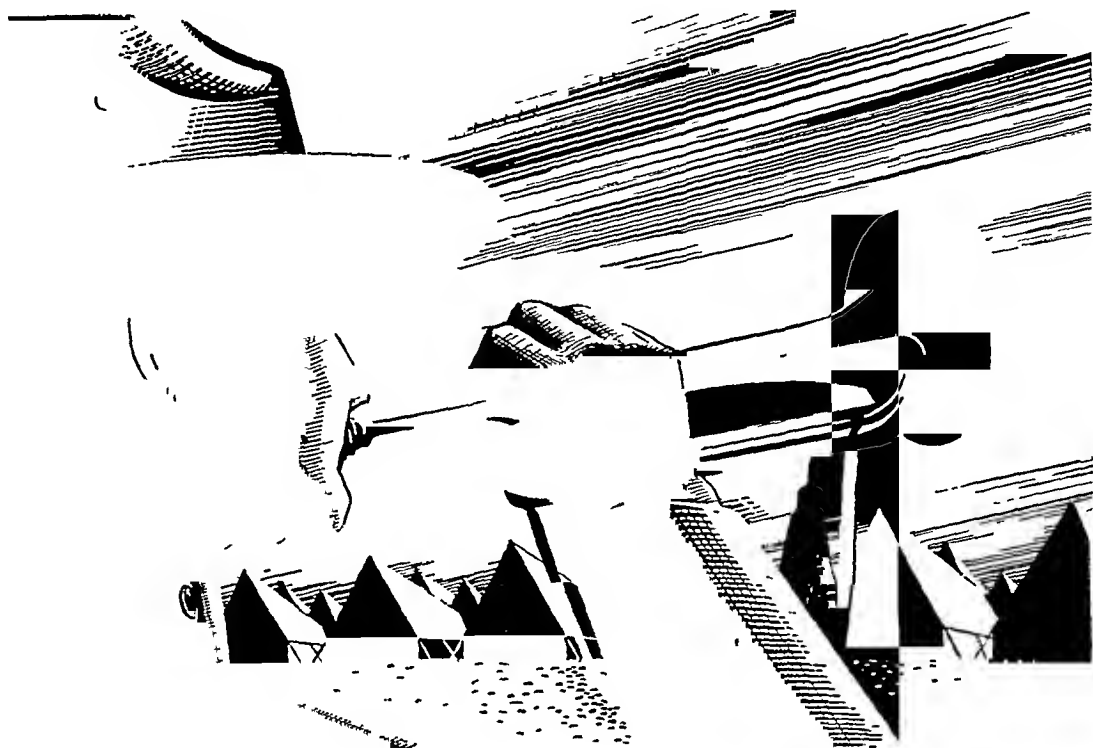
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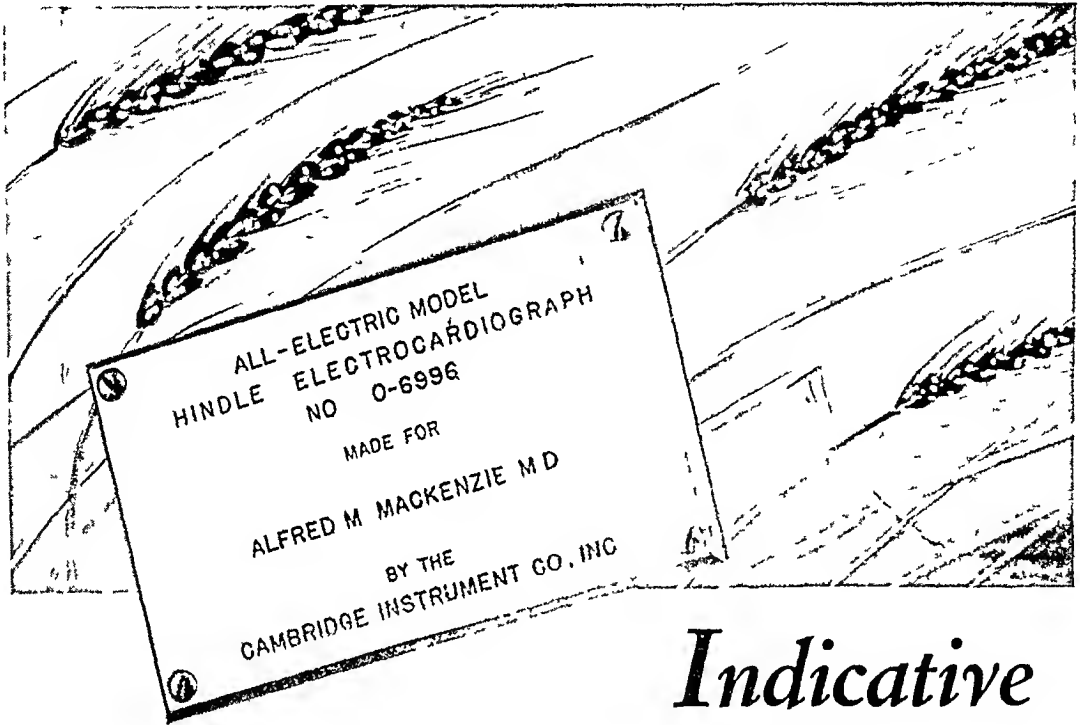
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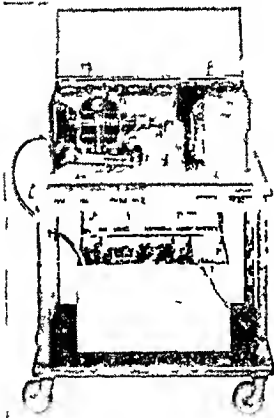
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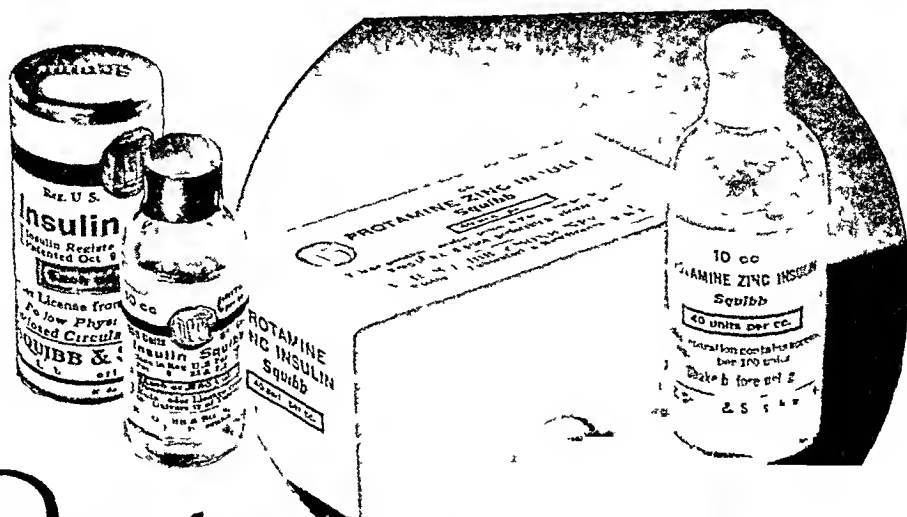
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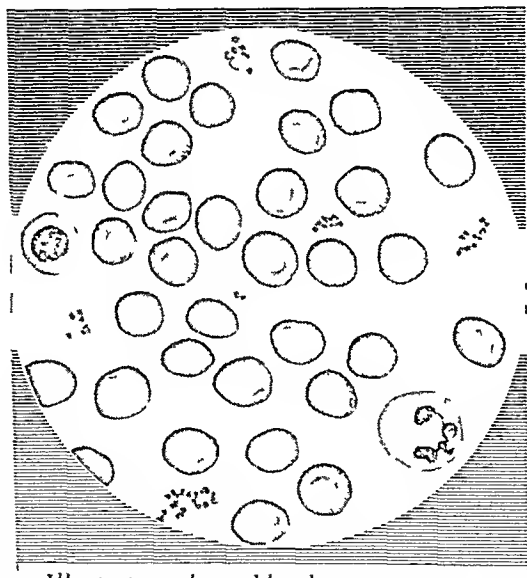


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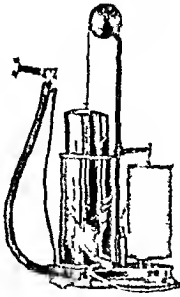
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ANNALS OF INTERNAL MEDICINE

VOLUME 11

SEPTEMBER, 1937

NUMBER 3

NUTRITIONAL FACTORS IN GRAVES' DISEASE

By J H MEANS, F A C P, S HERTZ and J LERMAN,
Boston Massachusetts

THAT marked grades of malnutrition may result from thyrotoxicosis has been long known. In 1893 it was that Friedrich Muller¹ noted the paradox of weight loss in the face of increased food intake and concluded therefrom that there must be in this disease an increased rate of katabolism.

Whether or not weight loss or general wasting will occur in Graves' disease depends on whether the appetite increase causes sufficient increase in the ingestion of total calories to offset the increased combustion. Compensatory hyperorexia we may call it. The bank balance, in other words, is determined by the relation of amounts deposited to those withdrawn. In Graves' disease we not infrequently encounter weight losses of as much as 50 pounds or more.

Not only, however, may thyrotoxicosis cause malnutrition, but lately it has come to our attention that malnutrition may cause, or precipitate, thyrotoxicosis.

A few years ago one of us (S H) was impressed with the number of patients with toxic goiter who gave histories of having started their thyrotoxic symptoms at the conclusion of a reduction program for obesity. An overweight person would go on a low calory diet and after having lost the desired amount of weight would increase the diet, but find that weight loss continued, perhaps at an accelerated rate. Along with this, nervousness, tremor and other symptoms of thyrotoxicosis would make their appearance. In some of these cases thyroid had been used to augment weight reduction, but in others, mere calory restriction.

Interest having been aroused in this sequence of events, we began to be on the lookout for such cases. They have turned out to be numerous. The total to date is 35. In 14 of these the prethyrotoxic weight loss was occa-

* Presented at the St. Louis meeting of the American College of Physicians, April 21, 1937.

From the Thyroid Clinic of the Massachusetts General Hospital.

sioned by reduction cures and in the remainder it was due to a variety of conditions such as restriction of diet in the treatment of ulcer, ulcerative colitis, diabetes and other diseases leading to malnutrition

It seems to us that this series is too large not to be of significance. Episodes which activate thyrotoxicosis have long been recognized. Psychic traumata, prolonged infections, accidents or physiologic strains, such as puberty, pregnancy or the menopause, fall in this category. Now it seems that acute malnutrition can be added. How it operates, we are not prepared to say, but it is not known how any of the others operate for that matter. It may be associated with changes in blood chemistry or with vitamin or protein deficiency.

In approaching the problem of the inroads which nutritional factors may play in the production of the clinical picture in Graves' disease it will be convenient to distinguish between what we may term general malnutrition due to total negative calory balance and more specific types of malnutrition, or deficiency due to absolute or relative shortage of specific dietary elements. Of general malnutrition, save insofar as it constitutes an indication for treatment, I need say nothing further, it being thoroughly familiar. Certain specific or special types of malnutrition, on the other hand, I believe can be discussed with some profit.

In this group of special forms of malnutrition let us consider first the *musculature*. Myasthenia is a common symptom in toxic goiter. Plummei,² Lahey³ and others have devised diagnostic tests to bring this symptom or sign into evidence. Actual muscle atrophy occurs less commonly, but in certain cases is very striking. Some years ago we⁴ reported a case in which there was a picture closely resembling progressive muscular atrophy in an advanced stage. The patient was also found to be suffering from toxic goiter. Cure of the latter by surgery was followed by recovery of the muscles. This is the most marked example of muscle atrophy we have seen in toxic goiter, but very often we encounter lesser grades with atrophy of the temporal, interossei or shoulder girdle muscles. Such atrophy is usually present in a patient who has been severely thyrotoxic over a long period of time and is therefore of prognostic significance. The exophthalmos, in certain types at least, may be a local expression of general muscle weakness. The degenerative changes in the striated recti muscles of the eye and the normal appearance of the smooth muscle of the eye, described by Askanazy,⁵ suggest a muscle imbalance which may explain exophthalmos. On the chemical side there is a disturbance in creatinine metabolism with creatinuria and, as shown by Shorr and Richardson⁶ a decreased creatine tolerance test.

The skeleton in certain cases shows marked decalcification. This is properly to be classed under specific forms of inanition. Aub and his co-workers⁷ in 1929 showed that the thyroid hormone causes a marked increase in the rate of withdrawal of calcium and phosphorus from the skeleton, without, however, in contrast to the parathyroid hormone, any sig-

nificant change in the blood levels of these elements. It is indeed in thyrotoxic persons that the highest levels of calcium and phosphorus excretion are to be found. This high excretion is a specific effect of the hyperthyroidism, not merely a feature of elevated general metabolism. (Aub et al¹)



FIG 1 Osteoporosis with compression fracture of a lumbar vertebra following thyrotoxicosis

found in cases of fever and leukemia with marked elevation in general metabolism, normal elimination of calcium.

The rate of decalcification of the skeleton in thyrotoxicosis will depend not alone on the rate of calcium loss, but upon the intake. Although the

increase in calcium excretion is great, it usually takes a long time for osteoporosis to become apparent. Patients with acute forms of toxic goiter usually get treated successfully before any marked grade of osteoporosis has been produced. The increased appetite probably causes an increased ingestion of calcium and offsets to some extent the process of bone wasting.

In a few cases of long-standing thyrotoxicosis, however, we have observed very marked osteoporosis, both in the spine and in long bones. In some of these cases symptoms have resulted, taking the form of deep aching pain in the extremities or back, and in one remarkable case there was a pathologic fracture of the body of a vertebra. This patient had been treated by us⁸ in 1919 for mild Graves' disease, then of three years' duration, by means of roentgen-ray therapy. She had improved somewhat, but, since she had not recovered completely, a subtotal thyroidectomy was done in March 1922. After that she was fairly well until August 1931, when while driving her car she was seized with sudden knife-like pain in the region of her lumbar spine. This persisted intensely and continuously for one and a half hours, then upon motion for three to four weeks and finally as tenderness in the lumbar region until December 1, 1931, when she returned to the hospital for study. Roentgen-ray examination showed marked decalcification of the entire spine and pelvis and a compression fracture of the first lumbar vertebra. The body was half its natural thickness and was irregular and mushroomed.

The patient was put on a high calcium diet with 5 drachms of calcium glycerophosphate and 30 drops of viosterol per day, under which regime her symptoms were quickly relieved. We have followed her since and although by roentgen-ray there is no great evidence of recalcification, the symptomatic result has been excellent.

Another striking example (a private patient of J. L.) is that of a woman of 58, who became bedridden as a result of long-standing thyrotoxicosis and cardiac failure. She showed a marked degree of osteoporosis. As a result of her semi-sitting position, she developed a dorsal kyphos and flaring of the lower ribs. The latter were exquisitely tender to pressure.

With removal of the thyroid, she has gradually assumed her normal activities and her heart is well compensated. Her kyphos has straightened considerably, the flaring of the rib margins is less and tenderness has disappeared. She is on an adequate diet with emphasis on milk, vegetables, cheese and meat.

In cases of long-standing thyrotoxicosis then, or even past thyrotoxicosis, in which pains in the spine or extremities are complained of, the possibility of osteoporosis should be given consideration and, if found, suitable treatment by a recalcifying regime instituted.

A shortage of iron is suggested in an impressive number of patients with thyrotoxicosis by the presence of nail changes of the sort characteristic of hypochromic anemia—that is to say spoon-shaped, brittle, lustreless and

longitudinally ridged—together with smooth tongues and gastric achlorhydria. Even when these signs are well marked, one usually finds but a slight degree of anemia. One patient recently, however, a woman of 58, presented symptoms of thyrotoxicosis, minimal eye signs and goiter, basal metabolic rate at the level of about plus 40 and along with all this, smooth tongue, spoon fingernails, achlorhydria, red count of 3.6 million and hemoglobin of 45 per cent. She was placed on both iodine and iron. She made a characteristic and good response symptomatically and metabolically to iodine, her basal metabolic rate falling to standard in nine days. She was continued on iodine for a year at the end of which time her basal metabolic rate was normal and she was symptom-free. The anemia also, in less than a month, rose to a red cell level of 6 million and hemoglobin of 75 per cent. Iron was then omitted. We presume that iron was responsible for the result. At the end of a year her blood picture showed a red cell count of 4.8 million and hemoglobin of 85 per cent.

Of late we have been interested in the question of avitaminosis in thyrotoxicosis. In the case of vitamin B₁, at least, Cowgill and his co-workers⁹ and others have shown that the need for vitamin increases in parallel fashion to the metabolic rate. Thus a person who had been receiving an adequate amount of vitamin B₁ during health might develop a deficiency on the same vitamin intake if he became thyrotoxic.

In view of these facts, two of us (S. H. and J. L.) administered vitamin B₁ in the form of Harris Yeast Powder to a small series of thyrotoxic patients and found that although it caused no change in basal metabolic rate, there was, coincident with its administration, a marked improvement in appetite and consequent gain in weight. Since that time we have employed treatment with yeast routinely in the preparation of thyrotoxic patients for operation. Although it is too early to draw a conclusion based on statistics of the effect of this maneuver on operative mortality, it is becoming increasingly clear that it is of value in improving general nutrition through the increase it causes in appetite. Its use is chiefly indicated in those patients whose appetite increase has been inadequate.

Shortage of vitamin B₁ may also play a more specific rôle in thyrotoxicosis. Weiss¹⁰ has shown that in alcoholics with cardiac insufficiency avitaminosis B₁ may play a rôle. It is quite possible, as he suggested to us, that it may also play a rôle in the cardiac insufficiency of thyrotoxicosis. Certainly one is more apt to see cardiac insufficiency in the malnourished than in the well nourished thyrotoxic patient. We recalled four recent striking examples as soon as Weiss mentioned the matter to us. One of these also had a moderate hypochromic anemia. Since iodine produces benefit in nearly any thyrotoxic patient, and since it is our practice not to withhold iodine in the thyrotoxic patient with cardiac insufficiency, we cannot say with certainty how much, if any, benefit to the heart vitamin B₁ administration has conferred per se. It will only be after large numbers have been treated that a dependable conclusion can be drawn.

Evidence of shortage of other vitamins has not been impressive. Scurvy we have not seen, but in one recent case in which thyrotoxicosis followed a grossly inadequate diet, night blindness became a striking symptom. It cleared up directly when an adequate diet was received. It may be interpreted as evidence of a shortage of vitamin A.

The chief point which we wish to make about all these matters, is that there is much more to the preparation of the thyrotoxic patient for operation than mere iodimization. The preparation, which we believe should be under the direction of the physician, but observed also by the surgeon, should include a positive attempt to improve general nutrition and relieve any specific deficiencies insofar as this is possible. Sometimes it will be the part of wisdom to defer operation, even though a good iodine response has been obtained, in order to meet more adequately a nutritional indication. The following case is a good example.

A 43 year old widowed supervisor of nurses, who had acute rheumatic fever at the age of 28, followed by mitral stenosis entered the medical ward February 16, 1936, with a story that for two years or more she had been running herself ragged, eating very little, taking a great excess of tea and coffee, sleeping badly, having marked anorexia and losing in 18 months some 25 pounds. She had been a thin, frail woman to start with and after the loss mentioned was markedly malnourished.

For two months prior to entry in addition there had been marked nervous irritability. At the time of entry she showed marked hyperirritability, slight bilateral exophthalmos, marked tremor, warm moist skin, tachycardia of 140, slight diffuse enlargement of the thyroid and a basal metabolic level of plus 30. Her heart showed the murmur characteristic of mitral stenosis, with normal rhythm. She weighed 106 pounds. Her tongue was sore and atrophic, but there was no anemia. Her red count was 5.0 million and her hemoglobin 90 per cent.

At this time one of us (J H M) made a note to the effect that she undoubtedly had exophthalmic goiter and that this appeared to have followed the development of a state of malnutrition also that although her thyrotoxicosis was mild she was a poor risk for surgery on at least three counts (1) because she had the complication of chronic rheumatic heart disease, (2) a very unstable psyche, and (3) a very severe grade of malnutrition.

She was given iodine and made a good response as far as symptoms went and her basal metabolic rate dropped to a normal level. Instead of operating at this point, however, it was felt wiser to send her home on iodine and high calory, high vitamin diet. She was given vitamin B in the form of Harris Yeast Tablets.

On March 19, 1936, she reentered, having gained seven pounds and become less nervous. A subtotal thyroidectomy was done on March 27, which she went through uneventfully and on April 4 her basal metabolic rate was minus 1.

She did well for about eight months, but then developed a mild recurrence of thyrotoxicosis which threw her heart into fibrillation. Iodine controlled the thyrotoxicosis adequately, but the fibrillation continued. In January of 1937 she went through a sharp attack of bronchopneumonia without thyrotoxic exacerbation or gross cardiac decompensation. Although it cannot be proved, our guess is that her course through thyroidectomy would have been far less smooth if she had been operated upon immediately after the establishment of iodimization.

In conclusion we should like to warn physicians and patients against too vigorous reduction cures for obesity, thyrotoxicosis may be induced thereby, and in the preparation of the thyrotoxic patient for operation we should like to urge that the possibility of nutritional disturbances be considered and, if found, that an attempt be made to correct them.

The manifestations of nutritional disturbance, which may be found in thyrotoxic patients, include, as well as general inanition, changes in musculature, skeleton, hematopoietic system and very likely in the heart and psyche. While these findings may be merely incidental and their causal relationship to thyrotoxicosis ascertainable only by an extensive statistical study we feel that they are of sufficient frequency to warrant consideration in the complete management of patients ill with Graves' disease.

The methods of correcting these defects include not only a high calory diet for relieving general malnutrition, but one high in vitamins and minerals as well. Vitamin B₁ may be of special significance as having appetite increasing proclivities, and also perhaps some special beneficial action upon cardiac function. We are now using Harris Yeast Tablets for this purpose. Pure vitamin B₁ preparations can be used when the indication seems urgent.

For the high calory intake the chief dependence should be placed upon carbohydrate. Excessive protein is undesirable because through its specific dynamic action protein raises metabolism. Carbohydrate, on the other hand, in large amounts is insurance against depletion of the glycogen stores of the liver and thus safeguards that organ. With regard to fat, there is no special indication that we know of. Fat may be given to whatever extent the patient's appetite demands.

We feel that there is good reason for regarding the malnourished thyrotoxic patients and the psychotic as well as those with cardiac insufficiency as poor operative risks. It is wise to get their weight curves at least started upward before permitting operation. This sometimes will require several weeks of pre-operative medical treatment. There is a tendency to rush thyrotoxic patients too fast to the surgeon. It is the physician's responsibility to see that this be not done. It is also his responsibility to avoid unnecessary delay in the securing of relief of thyrotoxicosis by operative intervention. Although it is desirable that he have certain definite routine procedures—the use of iodine, for example—it is also desirable that he study

each case as an individual problem and plan his actual therapeutic program to meet individual indications

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A STUDY OF THE DIAGNOSIS AND TREATMENT OF LOBAR PNEUMONIA ACCORDING TO TYPES AND SPECIFIC SERUM THERAPY *

By JULIEN E. BENJAMIN, M D , F A C P , MARION BLANKENHORN, M D ,
JAMES M. RULGSEGER, M D , and FANNIE A. SENIOR,
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ALTHOUGH recent reports of successes in the diagnosis and treatment of the pneumonias, according to specific criteria, have been impressive, it can hardly be said that the medical world is committed to the procedures. There are several valid reasons why this is true. While there have been excellent results reported by reliable observers in the treatment of the acute pneumonias with specific serum, the technical difficulties involved in accurate typing, as well as the expense incurred in the use of curative serum, are the major objections raised, and the ones which have caused clinicians to approach the subject with hesitation. These two obstacles will be overcome only when public health facilities are more widely distributed, so that laboratories, where typing may be done day or night, are more conveniently located, also funds must be made available for the purchase of curative serum, so that rich and poor alike may have its advantages. At present this is not true even of all cities of major size, to say nothing of the rural districts. Another possible reason why serum has not been more generally employed in the treatment of pneumonia is because of the doubts as to its efficacy, which many clinicians still harbor. In many instances the reasons for their scepticism appear well founded, and they will be won over only when serum therapy has arrived at the stage of infallibility.

The technic incident to correct, accurate, and rapid typing by the Neufeld method has been represented by enthusiasts as being an essentially simple technic, capable of accomplishment in any physician's office where technical assistance exists. It is quite possible that this explains some of the disappointments experienced by many reliable clinicians who have attempted the procedure. There is one thing that stands out with great certainty, namely, that if typing is not reliably done, the results in the administration of serum are bound to be disappointing. Whereas in a majority of instances the Neufeld technic is accomplished with little or no difficulty, in a certain percentage of cases difficulties will be encountered, necessitating arduous and painstaking study as well as special technical skill for their correct solution. When organisms are few in number, media suitable for the growth of pneumococci must be available (Avery broth or mice) so that the technician may find the invading organism which might otherwise be missed. Complete typing should also be instituted routinely, as in many instances two or even three types of pneumococci may be found in the same sputum. This infor-

* Read at the St. Louis meeting of the American College of Physicians, April 21, 1937

mation while puzzling at times, is of aid in the prognosis as well as diagnosis. Only in laboratories equipped with facilities not only for direct typing, but also for the transplanting of cultures to mocc and broth media, are satisfactory reports obtained.

While it is true that lives have been saved by the administration of serum at any time during the course of the disease, the greatest saving of lives occurs in those individuals who are fortunate enough to contract a type of pneumonia for which curative serum is available, and who are treated shortly after the inception of the disease. It should be possible, in the not too distant future, through a process of health education, to arouse public interest to the necessity of calling for medical aid early in the course of severe, acute respiratory disease. For the present, at least, this is not true and we are forced to treat situations as they exist. Furthermore, the disease unfortunately attacks in largest numbers those of the laboring class, and of these, the majority live under adverse conditions. Quite naturally, medical aid is not sought so early by this large group as by those in the higher economic level, where the disease is far less common. Practically all of the reported data concerning the specific treatment of the pneumonias have emanated from medical centers or large public hospitals. Had it been necessary to rely on the statistics gathered from private hospitals or in private practice, advances in this important aspect of the disease would have been much slower.

Those who have been closely associated with this method must admit that it represents the greatest advance in the control of this deadly disease, which has been made since pneumonia was first described.

Under the careful directions of such well known clinicians as Bullowa, Finland, Cecil and others, the mortality rate for the early treated cases of the commoner and more frequent types of pneumonia has been reduced as much as 50 per cent of its former high figure. In the more malignant types, and in the late cases the mortality rates have also been appreciably reduced. It was possible at the Cincinnati General Hospital in the year 1935 to 1936 to report the first series of 50 consecutive cases of Type I pneumonia treated within 96 hours of onset, without a single death.¹ These results were accomplished under anything but perfect conditions. The patients were inadequately nursed, the wards were considerably overcrowded, the patients were of the indigent class, many of them alcoholics. There was at hand, however, the setup for excellent laboratory work, and the enthusiasm for prompt and unrelenting administration of serum. We are now in our third year of study of the lobar pneumonias, according to this method. It is a critical analysis of some of our observations during the past 16 months which forms the basis of this discussion.

There are included in this study only the lobar pneumonias, with but few exceptions occurring in adults. It is primarily intended as a critical appraisal of the beneficial effects of concentrated specific curative serum in

patients whose pneumonic symptoms have existed 96 hours or less*. The treatment was instituted on the basis of Neufeld typing of sputum, mouse transplants and broth cultures. Commercial sera † for Types I, II, V, VII and VIII were used. There was also available, through the generous offer of the Littauer Pneumonia Fund, Harlem Hospital, New York City, serum for Types VI, XIV and XVIII. Blood cultures were taken in each instance, repeated when indicated, and the colony count followed.

The incidence of lobar pneumonia is quite high in Cincinnati. Morbidity rates are practically impossible to obtain, but each year there are more than 300 deaths attributed to this type of the disease, representing a mortality of 75.3 per 100,000 population. For the 16 months, October 1, 1935 to February 1, 1937, there were received at the Cincinnati General Hospital 485 cases (Table 1).

TABLE I
Cincinnati General Hospital
Incidence of Color, Sex, and Death Rates in Lobar Pneumonia
October 1, 1935 to February 1, 1937

	No. of Cases	Deaths	Per Cent
White	245	60	24.53
Colored	240	62	25.83
Males	344	79	22.96
Females	141	43	30.49
Total	485	122	25.15

Almost an equal number of white and colored patients were examined and treated, and they died in about the same proportion. There was a crude mortality rate of 25 per cent as against a crude rate of 30 to 50 per cent over a period of six years, studied by Schiff² prior to the general use of type specific serum.

The distribution of cases according to age groups is shown in table 2. It is noteworthy that although only 42 per cent of the total number appeared after the fourth decade, 67 per cent of the deaths occurred during those years.

* The time interval of 96 hours has been arbitrarily selected, because of the possibility of a spontaneous crisis occurring after that time. Our criteria for establishing the diagnosis of lobar pneumonia have been:

- 1 Typical acute cases (early)
 - (a) Sudden onset—chill, pain, fever, cough, rusty sputum
 - (b) Typing of sputum
- 2 Atypical and late cases
 - (a) History upper respiratory infection with sudden change as under (a) above
 - (b) Physical examination indicating consolidation
 - (c) Typing of sputum
 - (d) Roentgen-ray in all doubtful cases

In each instance, the subsequent findings on physical examination were always relied on as corroborative evidence of the existence of pneumonic consolidation. Further, more than one clinician examined each patient.

† One kind of serum was used throughout the investigation.

TABLE II
Cincinnati General Hospital
Incidence of Age and Death Rates in Lobar Pneumonia
October 1, 1935 to February 1, 1937

Decade	Number of cases	Percentage of incidence	Number of deaths	Percentage of total deaths	Percentage of deaths by decade
0-9	9	1.9	1	0.8	11.1
10-19	50	10.3	4	3.3	8.0
20-29	114	23.5	14	11.5	12.3
30-39	104	21.0	22	18.0	21.5
40-49	96	19.8	36	29.5	37.5
50-59	58	12.0	23	18.9	39.7
60-69	40	8.3	14	11.5	35.0
70-79	13	2.6	7	5.7	53.8
80-	1	0.3	1	0.8	100.0
Total	485		122		

In table 3 the cases are grouped according to serological types. Type I, the so-called "typical pneumonia," was responsible for 32 per cent of the entire group. Adding to this number, those other cases of the types for which curative serum exists (I, II, V, VII, and VIII), brings out the fact that for 66 per cent of the patients in this series appropriate curative serum was available.

Since only early cases were treated energetically with serum, a very considerable number of these patients did not receive this form of treatment. Of interest, however, are the results of serum treatment in some of these types.

We have worked on the thesis that there is no arbitrary dosage of serum in pneumonia, since so many factors must be evaluated in the treatment of the individual case. We have, however, set a certain minimal standard or range of dosage for each of the treatable types. These are Type I, 60-80,000 units, Type II, 100-120,000 units, Type V, 80-100,000, Type VII, 60-80,000 units, and Type VIII, 60-80,000 units. All of the "treated" patients received at least these amounts of serum intravenously. The initial dose consisted usually of 20,000 units, although in some cases it was only 10,000. The remainder of the minimal standard dosage was given at two hour intervals, each subsequent dose varying from 40,000 to 80,000 units. If blood cultures proved to be positive, from 60,000 to 100,000 additional units were administered, provided that the desired clinical effect had not intervened meanwhile.

Type I It has been shown conclusively that specific serum reduces the mortality in pneumonia due to Type I pneumococcus^{1,3}. While this is of the greatest importance, it is not the only criterion of the efficacy of serum. It is of equal interest to observe the effect of serum on the course of the disease in each patient. The uniformity with which rapid clinical improvement may be correlated with the administration of serum is of help, not only

TABLE III
Cincinnati General Hospital
Incidence of Types and Deaths in Lobar Pneumonia
October 1, 1935 to February 1, 1937

Type	No of Cases	Deaths
I	156 (32%)	25
II	52 (11%)	17
III	50 (10%)	28
IV	20 (4%)	1
V	47 (9%)	13
VI	9	2
VII	43 (8%)	6
VIII	30 (6%)	3
IX	8	1
X	2	0
XI	1	1
XII	13	4
XIII		
XIV	6	3
XV	1	0
XVI		
XVII		
XVIII	6	1
XIX	10	4
XX		
XXI		
XXII	2	0
XXIII	1	0
XXIV		
XXV	12	5
XXVII		
XXVIII	2	1
XXIX	1	1
XXXI		
XXXII		
Unclassified	12	6
Total	485	122
Crude mortality		25.15%

in evaluating the efficacy of this agent, but also in defining the limits of its usefulness. Therefore, these criteria will be briefly discussed.

In table 4 a comparison of serum treated and non-serum treated cases is shown. The reduction in the death rate was striking. The crude mortality holds for different seasons, according to age, sex, and the presence or absence of bacteremia, and with respect to the extent of the pulmonary lesion. Our series shows that the mortality rate for all types not treated with serum amounted to 31.5 per cent. It is also apparent that contrary to popular belief, Type I pneumonia is not a relatively mild type of infection, since in our series the mortality rate for the untreated cases was 26.5 per cent. The early serum treated cases of Type I had a mortality rate of only 4.11 per cent.

The effect of the serum on the course of the disease is no less impressive. Almost all of the patients favorably affected were much more comfortable within two to three hours after serum administration, and crisis was com-

plete or nearly so within 24 to 36 hours. While actual crisis was observed as frequently in the untreated patients who survived, undoubtedly its onset was materially hastened in those receiving serum. Examining for a moment those cases of Type I considered therapeutic failures, the following facts are revealed:

TABLE IV
Cincinnati General Hospital
Comparative Mortality in Serum and Non-Serum Treated Cases
October 1, 1935 to February 1, 1937

Type	Serum Treated within 96 hrs			Others *		
	No. of Cases	Deaths	Death Rate	No. of Cases	Deaths	Death Rate
I	73	3	4.1%	83	22	26.5%
II	26	8	30.7%	26	9	34.6%
V	11	2	18.1%	36	11	30.5%
VII	18	0		25	6	24.0%
VIII	8	0		22	3	13.6%
† XIV	2	0		4	3	75.0%
† XVIII	1	0		5	1	20.0%
Total	139	13	9.3%	201	55	27.3%

* A few of these patients received some serum, late in the disease, for experimental purposes.

† Obtained through the courtesy of the Littauer Pneumonia Fund, Harlem Hospital, New York City (Dr. Jesse G. M. Bullock).

Case 1 White, male, aged 78, admitted on the fourth day of the disease, with consolidation involving the right upper lobe. There was a history of previous coronary thrombosis, and evidence of auricular fibrillation. Marked nitrogen retention. White count 3,200 and later 1,900. Bacteremia of high degree. Died same day serum was given. He received 100,000 units.

Case 2 White, male, aged 65, admitted to the hospital with delirium tremens, and supposedly developed lobar pneumonia in the hospital. Leukocyte count 7,900. This man died with symptoms and signs of acute cardiac failure. There was also a question of beri-beri. He probably had had pneumonia longer than estimated. His death occurred on the same day that serum (118,000 units) was given. Necropsy revealed extensive empyema.

Case 3 White, male, aged 49. Second day of the disease. Blood culture positive after 100,000 units. Leukocyte count 6,500. He died the day after serum therapy. Doubtless, this patient should have received more serum.

The first two cases probably represent the irreducible minimum, since a certain number of derelicts and patients with severe degenerative diseases will inevitably succumb to the ravages of pneumonia, as the precipitating cause of their demise.

Whether or not a simpler and less drastic method of introducing antibody is suggested in years to come, we now have at our command a most reliable, specific, therapeutic agent to combat effectively that type of pneumonia which affects by far the largest number of people.

Other Types There is ample proof that specific serum is a reliable therapeutic agent in several other types besides type I. Certain features in

some of the types present minor difficulties, which have not been entirely obviated. In addition, the remaining 31 types, although their distribution is uneven, do not concentrate in any type in sufficiently large numbers to permit of reliable analysis. Caution must be observed in making deductions in so important a subject, with a relatively small number of cases. With this in mind, instead of subjecting each of the Types II, V, VII, VIII, XIV and XVIII * (the only other ones for which therapeutic serum is available) to critical analysis at this time it is of interest to consider the results obtained in these types considered together. Table 4 is valuable in this respect since it illustrates the saving in lives possible with this treatment. The numbers are sufficiently large to be significant. It is noteworthy that the mortality is three times as great in those patients who were not serum treated, as in those receiving serum.

Type II pneumonia is for us a difficult problem. Data at hand, gathered from the study of 52 cases indicate a comparable death rate of 30 and 34 per cent respectively, in cases treated specifically and non-specifically. In the final analysis it appears that in each unsuccessfully treated case, insufficient quantities of serum were given. The dose of serum for this type may ultimately be found to be three or more times the amount required for other types. In Finland's experience 200-300,000 units were necessary.⁴

Type V, it will be recalled, was the original Avery Type IIa. Nine per cent of our series fell into this type, a total of 47 cases. Of this number 36 were seen later than 96 hours after onset of their illness. None of these received serum and 11 of them died (30.5 per cent). Of 11 patients treated with serum earlier than 96 hours, only 2 died (18 per cent). Thus Type V is a pneumonia of high virulence when neglected, and quite amenable to specific therapy.

Type VII is often a fairly severe type of pneumonia which yields quite satisfactorily to serum administration. It is almost as prevalent as Type V. Of 18 consecutive cases treated early, not one succumbed, as against 6 deaths in 25 untreated cases (24 per cent).

Type VIII, related immunologically to Type III, is likewise favorably affected by serum therapy as far as anyone may judge from a small number of cases (30). No deaths occurred in the eight cases treated within 96 hours of the onset of pneumonia, there were three deaths among the 22 cases treated symptomatically. This type of the disease is, generally speaking, of the mild kind, if there be such in pneumonia, since the mortality rate was only 13 per cent for patients receiving no serum.

Bacteremia The importance of determining whether or not a blood stream infection is present, early in the course of pneumonia, cannot be overemphasized. No single factor influences the outcome so directly. The death rate in patients having bacteremia is exceedingly high. While the numbers here presented are not large, owing to the fact that we have taken

* Obtained through the courtesy of the Littauer Pneumonia Fund, Harlem Hosp., New York City. Dr. Jesse G. M. Bullowa rendered this and other valued help.

TABLE V
Influence of Bacteremia

Type	Cases with <i>Positive</i> Blood Culture		Cases with <i>Negative</i> Blood Culture	
	Number	Deaths	Number	Deaths
I	11 ⁵	9 ³	29 ¹⁵	1
II	11 ⁴	8 ³	19 ¹⁴	3 ³
III	10	10	23	5
V	7 ²	4 ¹	7 ²	0
VII	4 ³	0	18 ⁸	1
VIII	6 ³	2	9 ¹	1
Total	49 ¹⁷	33 ⁷	105 ⁴¹	11 ³

Superscript represents serum treated cases within 96 hrs

Death Rate—Cases with positive blood culture	67.3%
Cases with negative blood culture	10.4%
Serum treated cases with pos. Bl. Cl.	41.1%
Non-Serum treated cases with pos. Bl. Cl.	81.0%
Serum treated cases with neg. Bl. Cl.	7.3%
Non-Serum treated cases with neg. Bl. Cl.	12.3%

blood cultures routinely only since October 1, 1936, it is noteworthy that of 49 patients with positive blood cultures who did not receive serum, 81 per cent died. On the other hand of 17 patients with bacteremia who received serum within 96 hours of the onset of their illness, 41 per cent died. Undoubtedly this percentage is susceptible to considerable further reduction. We believe that such cases require two to three times the quantity of serum ordinarily administered. Further, the treatment must be continued until the blood is sterile. The importance of blood culture determination early in the disease is only second to correct typing of sputum, the one to determine specific diagnosis, the other as a guide to dosage of serum.

There is abundant evidence also that complications are related to the presence of bacteremia. During the past six months we have studied more intensively the influence of blood stream infection on the general course of the disease. In reviewing the commoner complications of the pneumonias for the period October 1936 to February 1937 the data obtained (table 6)

TABLE VI
Complications
October 1, 1936–February 1, 1937

	Bacteremic	Non-Bacteremic
Empyema	8	2
Meningitis	5	1
Endocarditis	4	0
Pyarthrosis	2	0
Pericarditis	1	1
Lung Abscess	1	2
Pleural Effusion	0	4
Otitis Media	6	0
Thrombo Phlebitis	0	1
Total	21	12

indicate in an interesting manner that the serious complications (empyema-meningitis-endocarditis) occur more frequently in the bacteremic cases

DISCUSSION OF SERUM THERAPY

The importance of giving adequate amounts of serum relentlessly until definite signs of improvement appear, cannot be overemphasized. The introduction into the blood stream of foreign protein in such quantities has produced very few unfavorable reactions. Indeed we have been amazed at the negligible number of thermal reactions and instances of serum sickness. This was doubtless due to the fact that the new concentrated and highly purified therapeutic serum was used. In all we observed 23 cases of serum sickness, and 19 cases which showed immediate reactions to serum, 8 slight, 9 moderate, and 2 severe. In one instance of a severe reaction, the use of serum was possibly contraindicated by a mildly positive skin test to horse serum.

In almost all favorable cases, very soon after the administration of serum, the patient's general condition improves. The cyanosis becomes less, the pulse rate usually falls and respiration appears less arduous. Then follows gradually a lowering of temperature, amelioration of other symptoms and within a few days the patient returns to a normal condition. What is equally important is that there is rarely extension of the lung lesion. The detoxifying effect of serum is frequently prompt and startling. Further, its sterilizing effect on bacteremia is worthy of note.

Effect on Resolution While the administration of serum causes no change in the rate of resolution of affected lung tissues, there is no evidence that this process is interfered with, or delayed. Certainly those individuals successfully treated remain in the hospital for a much shorter time than those non-serum treated. The days of intense suffering are also materially reduced.

Effect on Mortality The final test of the effectiveness of immune serum must rest on the evidence concerning the saving of lives. While the studies reported herewith do not represent a very large number of cases, the results compare most favorably with those reported by other observers. Undoubtedly the saving in lives is greatest in Type I infections, but in the other types as well the lowering of mortality rates of serum treated cases as against non-serum treated cases, is definite. It is not too radical to conclude that "no patient with Type I infection who dies without the early intravenous administration of large doses of Type I serum, can be said to have received the best treatment"⁵. There is abundant evidence that potent immune serum exists for types which together comprise 65 per cent of all lobar pneumonia. It is hardly adequate medical treatment if so many lives continue to be needlessly sacrificed.

According to Rogers,¹ there occur, annually in Ohio, in the vicinity of 3,000 deaths from lobar pneumonia, indicating about 12,000 cases. About

96 per cent of all cases of "lobar pneumonia" are pneumococcal in origin. Of the 12,000 cases 65 per cent, or 7,800 cases, may be assumed to be due to Type I, II, V, VII, or VIII. On the basis of our knowledge of the potential effect of serum, we find that 1,400 lives might be saved, a reduction of 46 per cent in the mortality from this disease. Although it is improbable for a variety of reasons that this goal can be attained in the near future, nevertheless we should be urged on by the fact that there exist today, therapeutic agents which make this achievement possible.

The difficulties in our path are largely those of lay education and public health organization. It is gratifying to note that the states of New York, Massachusetts, Connecticut and Michigan are now well organized in their approach to the prevention and specific treatment of the pneumonias. Facilities for prompt typing of sputum as well as appropriations for the purchase of serum for the indigent, exist as an important plank in their campaigns against preventable and curable diseases. While only specific serum for Type I and II is usually available, one of the states has already increased its funds so as to include Types V, VII, and VIII.

This represents a progressive attitude on the part of public health officials. Undoubtedly great reduction in pneumonia mortality will be the result of their efforts. The educational pamphlets distributed to the public and profession by these officials will go far toward rounding out their program of prevention.

That the pneumonias in a large percentage of instances are readily communicable from one individual to another is an accepted fact. For this reason, the enforcement of the same precautions as are taken in the effort to control the spread of other contagious disease is justifiable. Compulsory notification should be instituted without delay. Each case of pneumonia should be regarded as a focus for the spread of the infection, and the care of each patient should include those measures which have been found serviceable in other communicable diseases. We were convinced of the need of segregating patients in cubicles rather than treating them in the open ward and of requiring physicians and nurses to observe the same precautions in caring for these patients as are usual in contagious disease wards. The wearing of gowns and masks and washing hands after each examination or treatment should be strictly enforced. Before instituting these procedures, not a few instances of cross infection occurred in our ward. The type of pneumonia contracted was frequently traceable to patients in nearby beds. There were also encountered cases in individuals who had visited pneumonia patients in the hospital. We have likewise records of two or more members of a family contracting pneumonia of the same type in succession. Recently Finland and Tilghman⁶ emphasized this fact and in their conclusions stated that bacteriologic studies made on members of households in which multiple cases of pneumococcus infection were observed, revealed a high incidence of carriers of the type of pneumococcus responsible for the infections in the relatives.

CONCLUSIONS

1 Of 485 typed cases of lobar pneumonia observed during a 16 month interval, 66 per cent fall within those types for which therapeutic serum is available

2 Early diagnosis of the exact etiological agent of lobar pneumonia is of paramount importance in serum therapy, blood cultures are necessary, frequently as diagnostic procedures, and always for prognosis

3 In comparable series of Type I patients, the mortality among those receiving serum within 96 hours of the onset of the disease was 4.1 per cent whereas 26.5 per cent of the non-serum treated patients died. In much smaller groups of patients similarly striking results were shown after the use of specific serum in Type VII and Type VIII pneumonia respectively

4 Specific serum treatment of all patients (Types I, II, V, VII, VIII, XIV and XVIII) seen within 96 hours of onset, resulted in a death rate of 9.3 per cent. Of the group not treated with a specific serum 27 per cent died

5 Bacteremia influences the prognosis unfavorably and is an indication for the administration of larger quantities of serum

6 The intravenous administration of refined, concentrated antipneumococcus horse serum is not fraught with severe, untoward reactions in the non-sensitive patient

7 Lobar pneumonia is a contagious disease and as such should be treated as a public health problem

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SOME CLINICAL CAPRICES OF HODGKIN'S DISEASE

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IN 1856 Samuel Wilks¹ wrote, "It is only to be lamented that Dr Hodgkin did not affix a distinct name to the disease, for by so doing I should not have experienced so long an ignorance (which I believe I share with many others) of a very remarkable class of cases, a recognition of which would have guided both myself and others to an explanation of some more recent instances coming under our notice" Nine years later Wilks² critically analyzed Hodgkin's materials³ and found that the latter had included other pathologic conditions than the one bearing his name through the magnanimous gesture of the former An interesting confirmation of this position was afforded by Fox's reexamination of the original tissues⁴ after an interval of 97 years from the time of their preservation

If confusion marked the histologic definition of Hodgkin's disease, its clinical delineation could scarcely be expected to escape similar difficulties Eventually there have been evolved diagnostic criteria and clinical features that typify the classical case Briefly stated, Hodgkin's disease occurs characteristically in the age period between 18 and 35 years with a predilection for the male sex in the proportion of two to one Two secondary and minor peaks are observed in the incidence curves, namely between five and ten years for both sexes and at the menopause for women Insidiously the lymph nodes of a single group, as the posterior cervical chain, become involved in a singular manner They are painless and non-sensitive unless a nerve trunk be involved Their firmness varies with the cellular content, supporting framework and capsular tension As a rule it approximates the consistency of cartilage Until late in the course of the untreated subject the affected nodes remain discrete and unattached to the overlying or the underlying structures Redness and increased temperature of the skin are rarely observed over the involved nodes Suppuration is very unusual In the cervical involvement eventually a characteristic pyramidal conformation results with the largest nodes at the base above the clavicle and the smallest ones in the apex at the angle of the jaw⁵ Eventually the process becomes bilateral, involves the lymphoid system widely through the body and includes the liver and the spleen in its pathologic changes In general the involvement of the lymphoid tissues of the body is progressive but marked remissions with reduction in their bulk may occur spontaneously from time to time

The local symptoms of Hodgkin's disease will depend on the site of the lymphadenopathy They may include among other manifestations, paresthesias and pain from neural pressure, Horner's syndrome from sympathetic destruction, cyanosis and edema from interference with venous return

*Read at the St Louis meeting of the American College of Physicians, April 21, 1937
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(lymph stasis contributing), dyspnea, cough superior cyanosis and dysphagia from mediastinal involvement. Jaundice may result from common duct obstruction through lymphadenopathy or from direct invasion of the liver by the cellular reaction of the disease. Splenomegaly is a common manifestation and its degree may induce independent symptoms of dragging discomfort, early satiety and constipation. Hepatomegaly may lead to right-sided abdominal pain. Certain skin manifestations are encountered. Among these, brownish pigmentation and intractable pruritus take prominent places. A wide diversity of symptoms may result from the involvement of other organs or tissues.

The constitutional reactions of Hodgkin's disease are extremely variable. Fever occurs at some time in the course of practically all cases. In some it appears early and remains a prominent detail of the composite clinical picture. In others its appearance may be deferred to constitute a serious portent. Its form likewise is variable. Remittent fever is the rule but occasionally a continuous type is encountered. Finally there is a singular form of fever in this disease that is designated by the names of its several observers: Murchison,⁶ or Pel'-Ebstein.⁸ Such a fever is marked by bouts of remittent or continuous pyrexia and intermissions of apyrexia. Chills and sweats of varying degrees may attend the fever. While classically a remarkable regularity in the time and the degree of the febrile episodes as well as in the duration of the afebrile intervals may be anticipated, any recurring fever may assume a diagnostic significance in the presence of other clinical evidences of Hodgkin's disease. Tachycardia may occur independently, but usually parallels the febrile course. Cachexia appears sooner or later in most patients with Hodgkin's disease unless serious obstructive symptoms unduly shorten the course. Furthermore pallor and wasting are grave prognostic details.

The laboratory findings include the blood picture so adequately discussed by Bunting^{9, 10}. Beyond a question of doubt in the hands of expert hematologists his criteria offer a differential diagnostic aid of great usefulness in the presence of progressive lymph node involvement, but in the wider sense the transition from an early phase of lymphoid resistance to a late one of lymphoid paralysis affords a prognostic index of surpassing utility provided the blood has been followed consecutively with other clinical observations. An anemia of the hypochromic type is the rule and it may assume profound degrees. The platelets are increased in virtually all cases. The basal metabolic rate is elevated during the periods of clinical activity of Hodgkin's disease¹¹, but there is apparently no diagnostic implication in this observation. The ultimate diagnosis may in many cases rest upon the histologic examination of the affected lymph node. Certainly Gordon's studies upon the central nervous changes incident to the intracerebral and intravenous injections of emulsified lymph nodes¹² offer no material diagnostic assistance. The high incidence of mediastinal involvement¹³ indi-

icates the advisability of roentgenoscopy and roentgenography in the investigation of this field. Likewise roentgenograms of other suspected areas, as the bony framework, gastrointestinal system and so forth, may extend the clinical prospect.

Few clinical conditions conform more closely to the accepted descriptions than does the typical case of Hodgkin's disease. At the same time there is no disease with a more diversified range of clinical expression. On one hand these variants may result from the overwhelmingly predominant emphasis upon some common or uncommon feature of the disease. Again some clinical vagary may so distort the picture as to render its diagnosis extremely difficult.

With this thought in mind a series of such instances of Hodgkin's disease has been briefly digested.

I AGE

Case 1 A white female, aged 6, complained chiefly of coughing. This cough had persisted for five months without expectoration. There had been no weight loss but progressive weakness had been observed and breathing had become somewhat difficult. Two months after the onset and concurrent with an apparent respiratory infection, enlargement at the base of the neck on the left side was observed.

The physical examination established the presence of firm, movable supra-clavicular nodes on the left with dullness and bronchial breath sounds in the upper left chest. Below this, anteriorly, the breath sounds were absent but posteriorly the breath sounds were within normal range. The blood count was significant only in the polymorphonuclear neutrophilia of 87 per cent of a total leukocyte count of 8,150. Roentgenogram of the chest showed a mediastinal mass with extension to the left. Two months after the first admission the patient was reexamined and at this time fluid had appeared in the left thoracic cavity, and it proved to be serosanguinous upon aspiration.

Case 2 A white male, aged 84, entered with a chief complaint of "tumor of the neck," which condition was dated to a sore throat four years previously when a small purplish tumor was observed in the right tonsil. The occurrence of lymph node enlargement in the right side of the neck led to radium treatment of the tumor of the tonsil and surgical removal of the cervical masses. A year and a half later tumors recurred in the right side of the neck and later the left side was likewise affected. These progressed slowly and were removed surgically. Following their extirpation, roentgen-ray treatment was renewed, but after its discontinuance the tumors reappeared slowly and painlessly. The general health remained unimpaired and there was slight weight loss.

The physical examination was significant only in the definition of the cervical lymphadenopathy involving the submaxillary and the anterior and posterior cervical chains. These nodes were firm in consistency and irregular in shape. There was apparent attachment to the underlying structures but none to the overlying skin.

By reason of the extremes of age in Cases 1 and 2, six and 84 years respectively, Hodgkin's disease had not been a primary consideration and only upon biopsy was such a diagnosis possible.

II SKIN MANIFESTATIONS

A Pruritus

Case 3 A white male, aged 28, complained of shortness of breath. His trouble was dated to eight months ago when a troublesome itching developed over the entire body. Six weeks later a respiratory infection supervened and there was a relapse a week after its onset, so that the patient remained in bed for a week and a half. Following this, weakness persisted and vomiting became intractable. Four months after the onset, he went to the Rocky Mountains for a rest and fluid was found in the left pleural cavity. After an aspiration, the diagnosis of Hodgkin's disease was made by the biopsy of a cervical lymph node. The succeeding course was one of recurrent accumulation of fluid in the pleural cavity with progressive loss of ground.

The skin was particularly interesting in the encrusted, excoriated areas over the back and legs and the scarring and pigmentation at the site of old lesions. Lymphadenopathy of a characteristic order, splenomegaly and hepatomegaly with the evidence of mediastinal involvement ultimately completed the picture.

Pruritus is a well recognized manifestation of Hodgkin's disease. Not infrequently it succeeds other and more clearly defined evidences of the condition, but occasionally as in Case 3 pruritus may anticipate the characteristic lymphoid changes by a considerable period.

B Ulceration

Case 4 A white female, aged 26, experienced considerable difficulty in the healing of a wound subsequent to a biopsy in the left axilla three and a half years before admission. This study confirmed the diagnosis of Hodgkin's disease but subsequently cervical lymphadenopathy appeared and the characteristic pyramid of discrete, non-tender lymph nodes was noted. Extended roentgen-ray treatment was thereafter applied in both cervical and the left axillary regions. The left breast became involved and extension from the original site was suspected. With slight fluctuations the process was well controlled by roentgen-therapy, but in the intervals between treatment, sharp accessions in the process occurred in the above described areas. Twenty-seven months after the first observation in this hospital, the patient noticed a draining sinus in the right upper chest and there was progressive enlargement of the involved lymph nodes. Three subsequent admissions over the following 14 months showed some extension of the ulceration in the right infraclavicular region. This ulceration had a gray, dirty base with abrupt margins. A second supraclavicular sinus appeared. Eventually these two areas joined to form a single ulcer 10 by 12.5 cm. and the edges showed slight sluggish granulation.

Suppuration of the lymph nodes in Hodgkin's disease with resultant sinuses is unusual. Indolent ulcers on this basis are even rarer. Just what part roentgen-therapy played in the sequence of events in Case 4 is impossible to state. Unfortunately the earlier experience of the patient led her to refuse a biopsy of the margin and the base of the ulcer that might well have fixed the etiologic responsibility.

C Breast

Case 5 A white female, aged 58, complained of a lump in the breast which had been noted for a year. At first there had been a small lump the size of a hickory nut in the right axilla and this had grown to such an extent six months previously.

that she consulted a physician who advised amputation of the breast. The size of the mass alone inconvenienced the patient.

Through careful examination it became apparent the mass had arisen in the right axilla as stated by the patient and extended beyond the anterior axilla leading into the upper and outer segment of the breast and lying superficially to the pectoralis major. Posteriorly the mass extended across the axillary line to elevate the skin over the latissimus dorsi. It did not involve the apex of the axilla. In consistency it was firm but not of stony hardness. It was not attached to the skin nor to the deeper tissues. It was nontender and there was no general lymphadenopathy (figure 1).

Under general anesthesia the mass in the right axilla was resected and proved to be Hodgkin's disease.



FIG 1 Hodgkin's disease of the axillary lymph nodes erroneously diagnosed tumor of the breast (Case 5)

Particular interest attaches to Case 5 by reason of the mistaken diagnosis of a tumor of the breast, whereas an accurate history supported by a careful physical examination clearly traced the mass to its original site in the right axilla

III NEURAL INVOLVEMENT

A Neuritis

Case 6 A white male, aged 36, complained of pain in the right leg. For eight to ten weeks prior to admission the patient had experienced a constant dull ache in the calf of the right leg which made it impossible for him to straighten the leg. Shooting pains into the hip and thence down to the ankle on the posterior aspect of the leg had been experienced from the onset. These occurred chiefly in the night when the patient was in bed and lasted from 15 to 30 minutes. Heat and counter-irritants relieved the pain at first but later had no effect. More recently heat with massage seemed to give more relief. These pains had increased in severity and frequency, particularly in the week immediately preceding admission, until they had become practically continuous at the time of admission. Excessive sweating especially along the back had appeared.

There had been an appendectomy three months previously and at this time an intraabdominal mass had been determined. A cough had continued from the time of the operation and the mucus produced was occasionally blood streaked.

To physical examination pallor was evident. A few small, discrete, firm anterior and posterior cervical lymph nodes were noted. The axillary and epitrochlear lymph nodes were barely palpable. The spleen and liver were felt. There was also marked tenderness in the course of the right great sciatic nerve. A biopsy confirmed the diagnosis of Hodgkin's disease. The course was progressively downward during the hospital stay of 63 days, during which period the patient ran a widely remittent temperature, ranging from 99 to 104.8° F.

The blood picture was particularly interesting in that a terminal level of 24 per cent hemoglobin, 1,530,000 erythrocytes, 600 leukocytes, with 53 per cent neutrophils, 1 per cent eosinophils, 45 per cent lymphocytes and 1 per cent mononuclears was obtained the day before death.

The suffering of this patient from sciatic neuritis was extreme. The clear intimation of a neoplastic background lay in the determination of an intraabdominal mass at the time of the appendectomy. Hemoptysis, remittent fever, grave anemia and profound leukopenia completed the clinical picture in this subject.

B Herpes Zoster

Case 7 A white male, aged 40, complained of a lump in the neck. He stated that twelve years previously, he first noted swelling below the right ear. A tonsillectomy was performed and there was noted further enlargement of the mass after this time. "Electric" treatments thereupon reduced the swelling. Later there appeared lymphadenopathy in the axillary and inguinal regions. Adenectomy of the right axillary nodes was performed but upon admission bilateral cervical and axillary lymphadenopathy was apparent. The previously removed nodes had been diagnosed Hodgkin's disease. During the hospital stay, sensory disturbances occurred in the flexor aspect of the right forearm with paresthesias, burning and tingling giving way to deep boring pain. Areas of vesiculation appeared in the course of the cutaneous

nerves derived from C₈, T₁, T₂, and T₃ posterior roots and a diagnosis of herpes zoster was made (Figure 2)



FIG 2 Herpes zoster complicating Hodgkin's disease (Case 7)

Case 7 presented a classical picture of herpes zoster. In our experience this is an unusual complication of Hodgkin's disease in that it has been encountered in only two other instances. Histologic sections of the involved nerves or their ganglia are lacking and it may well be argued that its occurrence is a mere coincidence. Against this objection may be cited the relatively common involvement of the peripheral nerves in the process, particularly after roentgen-therapy.

IV BONE INVOLVEMENT

Case 8 A white male, aged 34, complained of a painless growth at the angle of the left mandible for a period of three years with rather marked extension in the eight months preceding admission. A biopsy confirmed the clinical diagnosis of

Hodgkin's disease Five years and eight months following this diagnosis, after an interval treatment with roentgen-ray, the patient returned with a complaint of sharp pains at the left side of the leg, beginning three months previously and later replaced by a pain in the back that remained localized until he grew tired and then radiating in a belt-like fashion around the anterior portions of the body There had been a weight loss of 12 or 15 pounds in the preceding month, and insomnia had been quite marked The roentgenogram showed a destructive lesion in the anterior portion of the body of the seventh dorsal vertebra with marked compression and wedging (Figure 3)

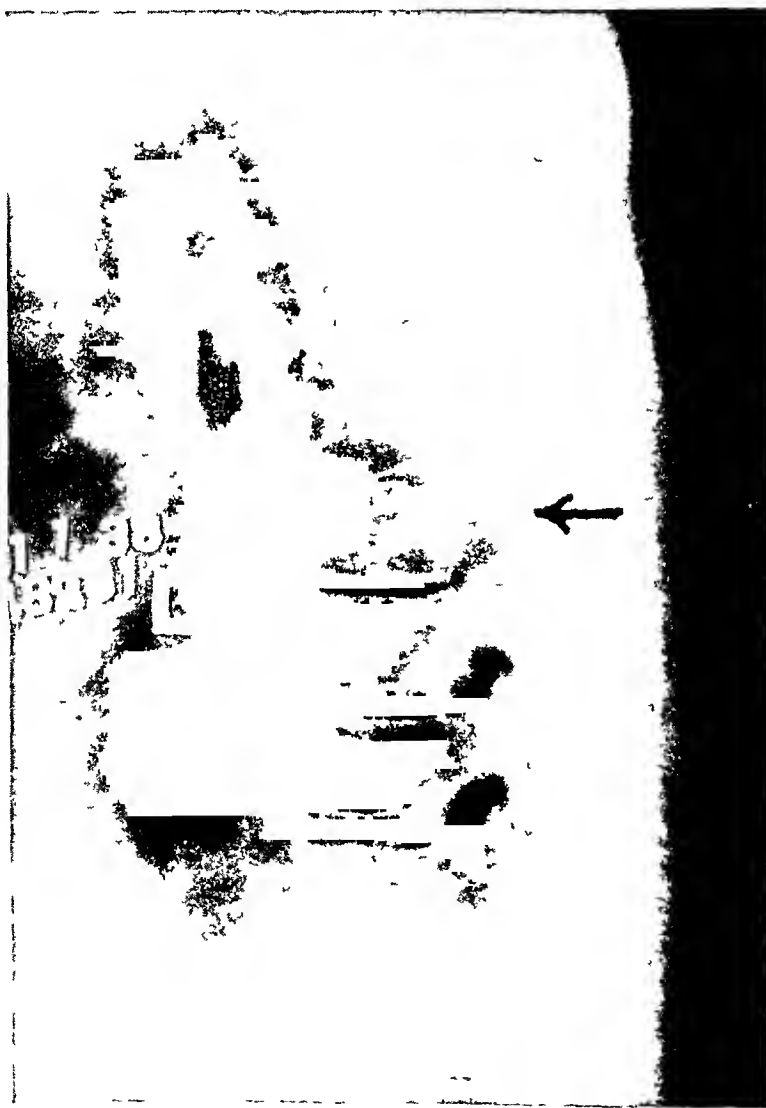


FIG 3 Hodgkin's disease of the thoracic vertebra (Case 8)

Case 9 A white female, aged 23, complained of "painful glands" in the left axilla This trouble had started four years previously in the lymph nodes of the neck A year before admission the nodes in the left axilla began to enlarge These had become progressively larger in size and definitely painful Weight loss had been

pronounced and weakness progressive Two years before admission pain was noted in the right knee and right hip and the left knee and left hip had likewise become involved Seven months before admission, there was a sharp pain in the left shoulder which lasted for four days At the same time the painful nodes in the left axilla increased the degree of disability in this shoulder A weight loss of 14 pounds had occurred in the preceding three years

The physical examination showed under-nutrition, discrete enlargement of the cervical lymph nodes, similar enlargement of the nodes in the left axilla and smaller nodes in the left epitrochlear region and marked limitation of abduction of the left shoulder Roentgen-ray of the left shoulder revealed an irregular destruction of the upper end of the shaft and the neck of the left humerus with irregular thickening of the cortex and bony spicules extending out into the soft tissues (Figure 4)



FIG 4 Hodgkin's disease of the head of the left humerus (Case 9)

Biopsy of an axillary node fixed the diagnosis of Hodgkin's disease The basal metabolism was plus 35 and plus 34 The blood count showed 50 per cent hemoglobin, 5,120,000 erythrocytes, 18,000 leukocytes with 94 per cent neutrophils, 3 per cent lymphocytes, 3 per cent metamyelocytes Relief from pain attended roentgen-therapy and she continued under observation for about two years

Cases 8 and 9 are interesting examples of the destructive bone lesions of Hodgkin's disease The implications in the latter are obvious, but in Case 8 there is the added significant detail of girdle pains on the basis of radicular involvement from destruction of the body of the seventh dorsal vertebra

V VISCERAL INVOLVEMENT

A Spleen

Case 10 A white female, aged 36, complained of weakness. There was a further history of cough succeeding a cold 17 months previously. This cough was non-productive and led to a pressing pain in the midabdomen. The appetite became progressively less. Two months after the onset of symptoms, the patient became pregnant. A weight loss of 17 pounds occurred in the ensuing month. Premature delivery at seven months was followed by improvement in appetite and some weight gain. Pain of a continuous and dull order augmented by eating was noted in the epigastrium 14 months before admission and at times this pain was so severe that even the weight of a blanket was uncomfortable. Four months before admission to the hospital, the pain had become more severe and weakness was progressive.

A medical consultation led to the diagnosis of an enlarged spleen, and because of the anemia, transfusions, iron and liver were prescribed. In spite of this support the symptoms progressed without abatement.

Physical examination revealed poor nutrition, icteric pallor, wasting, an epigastric mass, splenomegaly and hepatomegaly, bilateral axillary and inguinal lymphadenopathy. The existence of pruritus was suggested by extensive excoriations. The described lymph nodes were firm, discrete, non-tender and freely movable with relation to underlying and overlying structures. Later some enlargement of the cervical nodes became apparent. The roentgenogram of the chest showed some mediastinal involvement. The basal metabolic rate was plus 38 and plus 39. A biopsy of the axillary nodes showed the characteristic changes of Hodgkin's disease.

In Case 10 the spleen was palpably enlarged but its independent responsibility for the anemia and the epigastric mass was ruled out by a detailed study with the biopsy.

B Liver

Case 11 A white male, aged 39, complained of a growth in the left groin. Five years previously he had noted a mass the size of a walnut in the left inguinal region and there had been slight but steady increase in its size. Two weeks before admission there occurred a dull ache which was particularly marked when the thigh was flexed sharply upon the abdomen.

The physical examination showed pallor of the skin, exophthalmos, palpable thyroid gland, slight hepatomegaly, splenomegaly and inguinal lymphadenopathy. The biopsy of the inguinal nodes fixed the diagnosis of Hodgkin's disease. The basal metabolism was plus 22 and plus 24. Roentgen-therapy was instituted. After a period of 40 months, the patient returned with a history of the sudden appearance of jaundice a month previously. Anorexia, nausea, vomiting and weakness attended. The stools became clay colored and the urine highly colored. No abdominal pain was noted. In two weeks, 14 pounds had been lost. Reexamination noted the jaundice with a widespread nonpruritic, papular eruption, exophthalmos, palpable thyroid gland, palpable liver, submaxillary and axillary lymphadenopathy.

An obstructive jaundice was diagnosed from the clinical course, the absence of bile in the feces and of urobilin in the urine. Roentgen-therapy was instituted and after 400 r units to the right hypochondrium in two doses the patient became definitely more uncomfortable without perceptible change in the jaundice. Four days after the discontinuance of the roentgen-therapy, bleeding from the nose, lips, gums and gastrointestinal tract was noted. The stools were bright red from continued bleeding, and the patient died the succeeding day from blood loss.

Extrahepatic biliary obstruction from lymph node pressure upon the common bile duct seemed the simplest explanation for the rapidly developing jaundice in Case 11. Upon this assumption roentgen-therapy was initiated. At necropsy, however, the major biliary ducts were found to be patent, but an extensive cellular infiltration of the liver by the Hodgkin's process had determined the jaundice. Focal hemorrhagic areas were found throughout the intestinal tract.

C Retroperitoneal lymph nodes

Case 12 A white female, aged 27, complained of pain in the right side of the abdomen. The patient had known of the existence of a lump in the right kidney region prior to hospitalization. The symptoms were those of pressure in this area. She had gained weight and suffered no other discomfort.

The physical examination showed no palpable superficial adenopathy. An irregular tumor mass approximately 6 by 8 centimeters was palpated in the right flank. Fixed and painless, this mass was believed to be either an enlarged kidney or a tumor of the kidney. The laboratory studies, including special roentgenograms, gave no clue.

This patient was interesting because of the inability to fix a preoperative diagnosis, although the consensus favored a renal tumor. An exploratory operation established a lobulated retroperitoneal mass which was excised and proved to be Hodgkin's disease.

D Mediastinum

Case 13 A white female, aged 50, complained of discomfort in the abdomen which was dated to a dental extraction six months previously. A month later dyspnea appeared when lying on the left side and asthmatic attacks of a severe order would supervene. Relief resulted on turning to the right. This change of position would regularly stop the wheezing. Shortly after this, spontaneous dyspnea appeared and she became conscious of her cardiac action. On several occasions she had a sensation of fainting and would sit down to ward off impending syncope.

Physical examinations disclosed slight exophthalmos, cervical and submaxillary lymphadenopathy and evidences of a superior mediastinal mass with a small fluid accumulation in the left pleural cavity. The fluid withdrawn from the thorax was negative for tubercle bacilli. A biopsy confirmed the diagnosis of Hodgkin's disease.

Dyspnea is a common concomitant of mediastinal Hodgkin's disease, but Case 13 showed the added postural factor in the initiation and the relief of respiratory difficulty.

E Pleura (and mediastinum)

Case 14 A white male, aged 48, complained that "it was hard to breathe." Five and one-half years previous to admission, he had felt a mass in the upper left quadrant that became painful upon movement. Weight loss and weakness had progressed and there was slight enlargement of the lymph nodes of his neck. In the next six months, these became very large and firm but they remained painless. A diagnosis of Hodgkin's disease was made and roentgen-therapy induced marked improvement. According to the patient's story his health was perfect for a period of five years, but six months before admission the mass reappeared in the upper left

quadrant and the enlargement of the glands in the neck recurred. Embarrassment of respiration developed as a result of the cervical enlargement and roentgen-therapy was initiated. Dysphagia appeared about the time of onset of the dyspnea. The physical examination was particularly significant in the confirmation of the lymph node enlargement and the establishment of enlargement of the liver and spleen. Signs of fluid were found in the right pleural cavity and 1800 c.c. of slightly blood-tinged, straw colored fluid were removed by thoracentesis. Two weeks later another thoracentesis was done and the same amount of fluid removed. The blood count showed a mild hypochromic anemia. The basal metabolism was plus 25 and plus 24 at this time. A roentgenogram of the chest showed a lobulated mass above the cardiac shadow in the superior mediastinum. Fine reticular marking was noted through both lung fields. The right lung base was clouded by homogeneous density.

After several series of roentgen-ray treatments and a progressive decline in the general condition with only mechanical advantages from therapy, the patient died 10 months after the first admission. The leukocytes reached a low level eight months before death, or three months after the first observation in the hospital, at 1,660 with 46 per cent neutrophils, 40 per cent small lymphocytes and 14 per cent large lymphocytes.

Necropsy in Case 14 showed pleural and perisplenic involvement by the Hodgkin's infiltration in addition to the accustomed changes in lymphoid tissues.

F Lung (with cavitation and superior vena caval obstruction)

Case 15 A white female, aged 32, complained of a sick feeling. Earlier observations had established the presence of a pulmonary accumulation of pus and Dr. R. H. Jackson resected two inches of the anterior arc of the right fifth rib, sutured the visceral pleura to the parietal layer and two days later aspirated three ounces of purulent material from the subjacent lung. There was some gain in strength but no improvement in the general condition. The temperature was normal for three days after returning home but the cough continued and was productive of large amounts of yellowish pus. On one occasion, six weeks before admission, considerable bright red blood was expectorated. Herpes appeared on the tip of the tongue and on the mucous membranes of the mouth three weeks before admission. Substernal soreness developed and dyspnea occurred upon coughing.

The physical examination at the time of admission was significant in the emaciation and pallor of the subject. The chest findings included marked depression above and below the clavicles, particularly on the right. The expansion was reduced at the right apex and base. The tactile fremitus was decreased to absence below the right second rib. A hyperresonant note was determined throughout the left chest, but there was dullness almost to flatness in the anterior right chest below the clavicle. Over the area medial to the right midclavicular line and above the fifth rib, amphoric breath sounds and whispered pectoriloquy were heard. Interscapular impairment was determined on the right. After eleven days of study, Dr. R. H. Jackson completed a series of exploratory punctures of the right lung under gas anesthesia. Everywhere he met with dense resistance and only occasionally could withdraw a drop of thick muco-pus.

The further course of this patient was marked by progressive decline. Twenty-three days after admission the sternum became more prominent opposite the third costochondral junction, and this prominence was reddened and very sensitive. The right supraclavicular lymph nodes became palpable at this time and the lips and nail beds quite cyanotic. Three days later a second swelling developed in the thoracic

parietes over the right fifth rib about the midclavicular line. Night sweats made their appearance and were quite debilitating. Hemoptysis recurred. Edema of the feet advanced and eventually marked edema of the face appeared. A progressive increase in the venous pressure was noted in the veins of the arms. The prominence over the sternum increased and fluctuation was elicited over the same. Eventually there was some recession of this sternal protrusion. Dilatation of the veins in the right side of the abdomen and increased resistance in the right rectus were noted. Amphoric breath sounds eventually appeared beneath the right clavicle and as low as the second right interspace. The engorgement of the veins in the neck became a prominent feature as did also the edema and cyanosis of the head, neck and arms. She finally died nine months after the first observation in the hospital. From the time of her admission until death, she ran a remittent fever ranging from normal to 104° with a downward tendency of the curve in later weeks, when the range was from 96.4° to 100° . At necropsy, extensive mediastinal Hodgkin's disease was found with invasion of the lung and definite excavation of the process in the right upper lobe. There was likewise direct invasion of the lumen of the superior vena cava by the disease and thrombosis had led to the complete occlusion of this vessel.

The patient presented a difficult problem in diagnosis until accessible lymphadenopathy appeared. Early the presence of a suppurative process in the lung seemed unequivocal. Subsequent aspirations led Dr. Jackson to believe that the pulmonary process was neoplastic. Cavitation of the lung in Hodgkin's disease is not common, but its occurrence has been reported and the signs of excavation should not militate against the diagnosis. Superior cyanosis and edema are sufficiently distinctive to make the intravital recognition of superior vena caval obstruction relatively easy.

G Lung (with expiratory *souffle voilé*)

Case 16 A white male, aged 47, first seen in the Out-Patient Department with the complaint of a progressive, painless swelling in the neck, which a biopsy demonstrated to be Hodgkin's disease. The particular interest in this patient arose from the development of unusual signs in the right base ten months later. Evidences of mediastinal involvement (history and physical examination) had existed for six weeks, when there was observed a new phenomenon at the base of the right lung. A period of silence was noted over an area medial to and below the angle of the right scapula on expiration and then a peculiar rush of air and a shower of râles succeeded by an audible cough. This phenomenon persisted for several days and then gave way to an absence of breath sounds over this area. Subsequently, a pleural friction and then signs of fluid made their appearance at this base.

Upon necropsy, three months later, among other findings, the right main bronchus showed some erosion and there was an overgrowth of the mucosa here causing partial obstruction to the right lower bronchus.

A modification of the usual *souffle voilé* is described in Case 16 in that the apparent interference with a free passage of air occurred in the expiratory rather than the inspiratory phase of respiration. A mechanical explanation for this phenomenon was established at necropsy by the changes in the right main bronchus.

VI CONSTITUTIONAL MANIFESTATIONS

A General weakness

Case 17 A white male, 59 years of age, experienced spells of weakness, a run-down feeling and nervousness about three or four months before admission. This nervousness was described as manifesting itself by a quivering of the arms and by such a shakiness of the hands that writing was impossible. Five weeks before admission he accidentally discovered a firm mass the size of a golf ball in the right axilla, which in the intervening period had increased to the size of a baseball.

The constitutional symptoms in Case 17 suggested thyrotoxicosis rather than Hodgkin's disease, but the patient was admitted for study prior to the period of routine basal metabolic determinations in the lymphadenopathies and the diagnosis was reached through a biopsy of the right axillary lymph nodes. The elevation of the basal metabolic rate in the active periods of Hodgkin's disease may at times confuse the diagnostic issue.

B Suspected focal infection

Case 18 A white female, aged 29, complained of a cough which began a year and a half before, when she began to feel listless and gradually lost weight from an average of 100 pounds to 90 pounds. Her teeth were held responsible for this decline and all teeth in the upper jaw were extracted 14 months before admission. Five days later, swelling in the nodes of the neck was observed and a cough developed which continued dry and unproductive. After a month's time, all of the teeth in the lower jaw were extracted and although there was some subjective improvement, enlargement of the cervical lymph nodes persisted. Five months after this, the symptoms of weakness had progressed markedly and a tonsillectomy was performed. In spite of the surgical procedure, the cervical nodes progressively enlarged and the dry cough continued. Five months later a biopsy was performed and the diagnosis of Hodgkin's disease made. The roentgenogram of the chest confirmed the physical evidence of a superior mediastinal invasion.

This patient had the common experience of many individuals with Hodgkin's disease, in whom an exhaustive search for a focal infectious explanation of the constitutional symptoms proves futile and the diagnosis ultimately is derived by exclusion or by an opportune biopsy.

C Suspected tuberculosis

Case 19 A white female aged 26, complained of choking in the neck. She had felt quite well until 11 months previously except for an increasing susceptibility to colds. Succeeding one of these attacks there were marked pleuritic pains in the right chest and these continued from time to time in the interval until her admission. Lack of energy was likewise noted and at the time of admission, she was beginning to have difficulty in breathing, and choking when lying on her back. The complaints had become progressively worse. Enlargement of the nodes in the neck likewise progressed but there had been some subsidence of the swelling immediately to the left of the sternum. On suspicion of tuberculosis she had been admitted to the sanatorium two months before and had been a bed patient. Constant irritating cough had occurred and there had once been a hemoptysis of one-half cup of bright red

blood. Marked night sweats, fever, dyspnea on exertion and a slight irregularity of cardiac action had been reported.

The past medical history added only the significant details of recurrent tonsillitis and "scrofula" in childhood. The family history disclosed a tuberculous background, the father having died of tuberculosis, a sister and a cousin likewise suffered from tuberculosis.

The patient was unable to lie upon her back. The hands were cool and moist and there were scars in the neck. The anterior and posterior cervical lymph nodes were enlarged. The supraclavicular nodes were particularly prominent. There was slight suprasternal bulging. The described nodes were firm and apparently discrete. There was dullness at the left apex with some impairment at the right base. The breath sounds over the left apex were quite distant. The roentgenogram of the chest showed a dense shadow in the superior mediastinum, largely obscuring the cardiac outline. A dense shadow with an irregular upper border was noted at the right base and a less extensive density at the left base. A biopsy of the cervical nodes established the diagnosis of Hodgkin's disease. A thoracentesis on the right removed 650 cc of fluid.

Case 20 A white male, aged 24, complained of pain in the chest. Indefinite gastric symptoms had existed for a year but the pain in the chest dated only five weeks past. A cough with chills and sweats was noted at the onset and there was a severe pain in the upper anterior chest, apparently beneath the sternum. Cough was of a dry unproductive type, and a remittent fever with chills and sweating appeared daily. The patient was confined to bed for two weeks and then began to move about the house occasionally. The dry cough persisted. There was pain in the chest which extended to the lower sternal region. Dyspnea appeared and he was returned to bed under the attendance of his family physician. By the fourth week, the cough became productive of mucus without blood-streaking. He was referred to a tuberculosis sanatorium but the medical director sent him to the Wisconsin General Hospital where evidences of cervical adenopathy and of a pleural effusion on the right were established. One thousand cc of fluid were removed from the right pleural cavity whereupon a coarse pleural friction became audible at the base. Bacteriologic studies and animal inoculation of this fluid showed no tubercle bacilli. The biopsy of a cervical lymph node established the diagnosis of Hodgkin's disease.

Cases 19 and 20 illustrate those frequent instances in which tuberculosis is suspected in patients suffering from Hodgkin's disease. In Case 19 the past medical and family histories clearly justified this thought. Furthermore frank hemoptysis had once occurred. Chest pains, cough, fever and sweats completed the masquerade in both cases.

D Suspected undulant fever (or tuberculosis)

Case 21 A white male, aged 35, complained of "pain around the stomach." His complaint began three months before when he experienced the feeling of oncoming gripe. Following this there was a loss of energy, and a week later coughing in the morning and evening was noted. Two weeks later the appetite was sharply reduced and there were gas pains. Weight loss became apparent and weakness supervened. After slight exertion he felt extremely exhausted and perspired profusely. A month previous to admission he again consulted a physician who told him that he was running a fever and sent him to bed. After that time, his temperature had ranged from 100° F in the morning to 102 or 103° F in the evening. He was suspected of

being tuberculous and sent to a sanatorium where he stayed for several days, but negative chest findings led to his discharge

A further confusing factor entered the story in the occurrence of undulant fever in the wife the previous summer. Her complaints had grossly paralleled the patient's. Because of the general occurrence of Bang's disease in his herd he had disposed of all cattle, cleaned his barns and procured a new herd with the exception of the few animals in the first group that had not had positive reactions. However, he had stopped boiling milk about a month prior to the onset of his symptoms.

Physical examination disclosed marked emaciation, a mass in the right axilla (which the patient thought had been present for eight years) and a small mass in the left supraclavicular fossa. There were likewise many small nodes in the right supraclavicular fossa. These described masses were non-tender, firm in consistency, and freely movable. The liver and spleen were palpably enlarged, the former extending 8 cm. below the costal margin and the latter 11 cm. The blood count on admission was 48 per cent hemoglobin, 2,050,000 erythrocytes, 4,500 leukocytes, 75 per cent neutrophils, 24 per cent lymphocytes, 1 per cent monocytes. A low level of leukocytes occurred three weeks after admission at 2,650, with 80 per cent neutrophils, 14 per cent lymphocytes and 6 per cent monocytes. A remittent fever with a range of 98 to 104° marked the hospital stay of 42 days and the patient died. Biopsy as well as necropsy findings confirmed the clinical diagnosis of Hodgkin's disease.

The constitutional symptoms had suggested the possibility of tuberculosis in this patient. The coincidence of undulant fever in his wife further confused the issue, particularly since their clinical pictures superficially tallied. The general lymphadenopathy, splenomegaly and hepatomegaly at the time of admission to the hospital simplified the problem and the biopsy clinched the diagnosis of Hodgkin's disease. The anemia and leukopenia in this patient should be especially remarked.

E Alternating pyrexia

Case 22 A white male, aged 50, complained of a fever of eight months' duration. Actually this patient had not been well since a respiratory infection 11 months before admission, but the febrile reaction began three months later. The first episode of fever lasted for five days and was attended by malaise and aching pains. Since the original attack, there had been recurrences of fever at intervals of four to eight days and the febrile episodes themselves had lasted from one to four weeks. There had been no severe shaking chills but usually the attacks were preceded by a chilly sensation of the back and the temperature ranged from 97 to 104° F. with considerable daily variation. The malaise and general aching had continued with the bout of fever. For a few nights before admission, he had regularly been delirious during the height of the fever.

The physical examination established a cervical, axillary and inguinal lymphadenopathy. The spleen was definitely enlarged. Biopsy of one of the cervical nodes confirmed the diagnosis of Hodgkin's disease. During the period of hospitalization, fever occurred at irregular intervals. The temperature ranged from 98.2 to 103.2° F. in febrile periods which lasted 13 and 14 days, respectively, and the one afebrile interval was of 12 days' duration. The patient left the hospital in a second afebrile period, which had then lasted five days.

Case 23 A white male, aged 11, gave a history of lymphadenopathy of two years' duration involving particularly the cervical region. A biopsy fixed the diagnosis of Hodgkin's disease and particular interest in this patient attaches to the febrile

course upon the fourth admission. At this time a definitely alternating pyrexia was observed with periods of remittent or continued fever ranging as high as 105° F and lasting for 11 to 18 days and afebrile periods of 7 to 15 days (Figure 5)

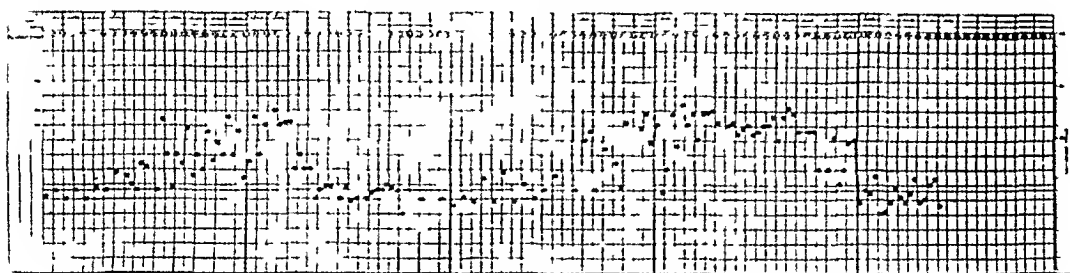


FIG 5 Alternating pyrexia (Case 23)

Case 24 A white male, aged 37, presented himself because of difficulty in breathing and dated his disability to an attack of pneumonia two years previously. Strength had never been regained from that time and six months before admission he experienced a respiratory infection with chills and fever as high as 103° F. During the past month there was recurrence of the fever and severe pain extending down the right leg. Paresthesias of the feet had occurred the year before. There was a history of roentgen-therapy for masses in the neck a year prior to admission. For a few days there had been a sudden impairment of hearing with headaches. Night blindness had been noted for four or five years.

Physical examination revealed a peculiar dusky pallor with unusual apprehension, restlessness and frequent twitchings of the hands and feet, widening of the palpebral fissure and slight exophthalmos, left cervical lymphadenopathy, splenomegaly and hepatomegaly. The blood count showed 58.4 per cent hemoglobin, 3,015,000 erythrocytes, 5,413 leukocytes with 83 per cent neutrophils, 0.6 per cent primitive cells, 6.8 per cent lymphocytes, 7 per cent monocytes and 2 per cent large young cells. The eyegrounds showed the characteristic changes of retinitis pigmentosa.

The most significant detail in this patient's clinical course was the continued fever ranging from 103 to 104.8° F for nine days and then followed by lysis over a six day period to normal. Temperature was maintained at this level for the remaining ten days of the first hospital stay. When he was readmitted 22 days later, another bout of fever was encountered, ranging from 102 to 105° F until his death three weeks later. His blood count six days before death was 57 per cent hemoglobin, 2,770,000 erythrocytes, 8,800 leukocytes with 94 per cent neutrophils, 5 per cent lymphocytes and 1 per cent monocytes.

The term, alternating pyrexia, was suggested by Gowers¹⁴ and it is accurately descriptive. At the same time it avoids the controversial issue of priority in the definition of the remarkable bouts of fever interrupted by afebrile seasons in this disease. An erroneous impression should be corrected. While the alternating pyrexia has definite diagnostic value in Hodgkin's disease, it is the least common type of febrile reaction to this condition. Remittent fever is much more common and continued fever is not unusual. As stated before, a fixed regularity in the form and the duration of the phases of alternating pyrexia of Hodgkin's disease may be predicted at times. As a rule the fever is remittent in such bouts. In these details Case 22 falls close to the rule, but Cases 23 and 24 are exceptions. Case 23

ian the alternating pyrexia as a terminal picture and Case 24 had recurrent bouts of continued fever of striking constancy. In any event the diagnostic significance of alternating pyrexia in the presence of even suggestive evidence of Hodgkin's disease should not be overlooked.

VII BLOOD

A Anemia

Case 25 A white male, aged 39, complained of shortness of breath. The present condition was initiated five months previously by pain in his arms extending to his finger tips and a sensation of numbness in the latter. The pain was usually aching and occasionally accompanied by similar discomfort in the legs. "Fatigue aches" the patient termed them. Shortness of breath had progressed and dizziness was observed in the morning on rising. There had been a sore mouth two years previously, relieved by repair of the teeth. Soreness of the tongue over the past year had responded to brushing of the teeth with soda. Extreme night sweats had appeared over the past three months and there had been chills with sweats. Palpitation and dyspnea had advanced steadily as had also the paresthesias.

The physical examination included a yellow pallor, palpable liver and spleen. A few inconspicuous inguinal and epitrochlear nodes were noted.

The laboratory examinations included the blood count: 40 per cent hemoglobin, 1,170,000 erythrocytes, 2,900 leukocytes without a significant differential change. The gastric analysis showed no free hydrochloric acid, even after the injection of histamine. The icterus index was 8. Urobilin in excess was found in the urine. The basal metabolic rate was plus 30 and plus 29. A diagnosis of pernicious anemia was made. Concentrated liver extract administered parenterally at five-day intervals effected no improvement in the general condition. Because of the poor condition of the patient and the failure of response to liver, a transfusion was done 15 days after admission. A continued observation of the marrow insufficiency, anemia, leukopenia and thrombocytopenia, attracted attention and it was furthermore significant that the improvement from transfusions was not maintained. Finally, 88 days after admission, a small lymph node in the left posterior cervical chain was noted, a biopsy obtained and the diagnosis of Hodgkin's disease made. Whereupon roentgen-therapy was initiated and the earlier advantage of transfusions became very much more pronounced in the improvement of the blood picture. A month later the following level pertained: hemoglobin 70 per cent, erythrocytes 5,140,000, leukocytes 6,850.

The erroneous diagnosis of pernicious anemia in this patient was not discovered until the failure of response to adequate liver therapy led to a search for an explanation. The hypochromic anemia, pigment changes and achlorhydria all added to the confusion. The palpable spleen should have aroused suspicion, but only upon failure of specific therapy was a lymph node excised and the diagnosis of Hodgkin's disease made. The response of the blood picture to transfusions after roentgen-therapy was as spectacular as the subjective improvement.

B Leukocyte formula in prognosis

Case 26 A white female, aged 41, complained of weakness. Eighteen months previously she had suffered from a sharp rheumatic pain in the right arm, radiating from the shoulder to the elbow and aggravated by motion. This pain continued in

severe intensity for a month and then disappeared to return with cold weather and hard work. For several months before admission the pain had persisted and the patient noted firm lumps in either side of the neck. With effort, as in doing the family washing, the right arm would swell, become blue and paresthesias would occur without actual pain.

The physical examination determined the presence of a pyramid of discrete, non-tender lymph nodes in the cervical region with the base at the angle of the jaw. The largest nodes were in the upper end of the chain. Axillary lymphadenopathy and inguinal involvement were evident to physical examination, and mediastinal involvement to roentgen-ray. Upon repeated examinations during the succeeding nine months, the blood count ranged from the initial level of 65 per cent hemoglobin, 6,590,000 erythrocytes, 23,200 leukocytes, 88.2 per cent neutrophils, 1 per cent eosinophils, 6.6 per cent lymphocytes, 4.2 per cent monocytes, to a level of 40 per cent hemoglobin, 3,260,000 erythrocytes, 31,800 leukocytes, 96 per cent neutrophils, 2 per cent lymphocytes and 2 per cent monocytes twelve days before death.

From Bunting's work^{9,10} the leukocyte formula in Hodgkin's disease assumes an exceedingly important place in the prognosis. Clearly the isolated numerical leukocyte count means little in any condition and in this disease a single differential picture avails nothing, but by repeated determinations in skilled hands it is possible in conjunction with the clinical findings to trace the stages and to predict the outcome of this disease with a measure of assurance. The patient passes from a stage of lymphoid resistance with an inversion of the formula to that of lymphoid paralysis when in a terminal period the neutrophils may number as high as 98.5 per cent of a grossly elevated leukocyte count.

C Suspected leukemia

Case 27 A white male, aged 39, complained of distress after meals. Until three years previously he had been entirely sound and then suffered from neuritis and a "tired feeling." Tonsillectomy was performed and the patient was much relieved for six months, whereupon early fatigue returned. For 10 months night sweats appeared practically every night. Eight months thereafter thyroidectomy was performed with some temporary improvement. Two months prior to admission he began to lose ground again. Sweats returned nightly and there was considerable distress after meals. A sense of pressure developed half way through the meals and remained two or three hours thereafter. This feeling of distress appeared after every meal. There was a 10 pound weight loss before admission.

The physical examination revealed a sallow complexion and red beefy tongue with prominent fungiform papillae. Marked enlargement of the liver and spleen and free fluid in the abdomen were noted. A few supraclavicular nodes were palpated. The blood count on admission showed 55 per cent hemoglobin, 3,690,000 erythrocytes, 58,000 leukocytes, 92.75 per cent neutrophils, 0.25 per cent eosinophils, 4.5 per cent lymphocytes and 2.5 per cent metamyelocytes. Basal metabolism was plus 32 and plus 35. A high point in the leukocytes was reached 13 days after admission at 71,000, 91 per cent of which were neutrophils.

A diagnosis of chronic myelocytic leukemia was maintained for some time until the persistence of the above leukocytic formula, remittent fever, lymphadenopathy and the clinical course necessitated a review of the im-

pression and the consideration of Hodgkin's disease. A biopsy confirmed this diagnosis.

D Leukopenia

Case 28 A white male, aged 35, complained of swelling of the "glands" in his neck, which dated back three months and was first noted as a part of a general lymphadenopathy. After a period of roentgen-therapy in the hospital, he was treated as an outpatient on two occasions over the next six months. An interval of eight months elapsed before a readmission, at which time he reported an interval of freedom of symptoms and of regained weight and strength during the summer of the previous year. With the return of cold weather the lymphadenopathy had recurred and there was pain in the left lower quadrant. Weakness and fatigue marked the subjective picture at this time. There was general lymphadenopathy and hepatomegaly. A further series of deep roentgen-therapy was administered at this time. The patient returned to the hospital four months later with a history of further fatigue and bleeding of the gums. After a rest period of a month, he returned obviously in a sharp relapse with marked pallor, marked exophthalmos, enlarged liver and spleen and general lymphadenopathy. The interesting change in the advancing anemia and leukopenia reached an extreme point in the latter detail with 450 leukocytes, 35 per cent neutrophils and 65 per cent lymphocytes, three days before death. At this time the hemoglobin was 45 per cent and the erythrocytes 2,490,000.

Naturally the contribution of roentgen-therapy to the profound leukopenia in Case 28 must be seriously considered. In our judgment it was an important factor in this instance, but the natural occurrence of a grave leukopenia has in several other patients led to a suspicion of an aleukemic leukemia and the necessity for a marrow biopsy where accessible lymph nodes were not enlarged. Boyer's recent review of leukopenia in Hodgkin's disease¹⁵ is very illuminating.

VIII CONCURRENT TUBERCULOSIS AND HODGKIN'S DISEASE

Case 29 A white male, aged 48, gave the history of axillary lymphadenopathy of seven years' duration, succeeding a felon on a finger of the left hand. Removal of a lymph node from the left axilla ten months after the onset led to a diagnosis of Hodgkin's disease. After a further interval of eight months more nodes reappeared in the left axilla and grew to the size of a grapefruit. Roentgen-therapy led to some subsidence, but there was later enlargement of nodes in the right axilla and also in the cervical region. Further roentgen-therapy was applied but the nodes had recurrently appeared in intervals between the treatment.

Upon physical examination the nodes in the cervical region were small, discrete and non-tender. Similar nodes were defined in the inguinal region. The nodes in the axilla, however, were slightly tender, confluent and adherent. The biopsy was illuminating in that the coexistence of tuberculosis and Hodgkin's disease was established.

Case 29 merely substantiates Ewing's statement, "Tuberculosis follows Hodgkin's disease like a shadow"¹⁶

This brief review of the experience in one clinic emphasizes the necessity for diagnostic awareness of the possibility of Hodgkin's disease in a

number of guises. Clearly the clinical pattern must not be too sharply drawn or many cases will escape early recognition. The constitutional and hematopoietic reactions of the disease appear to be especially susceptible of misinterpretation unless the diagnostic consciousness of these possibilities be ever present at the bedside. Finally the laboratory aids to the diagnosis should be regularly invoked. The blood picture, in expert hands, has certain diagnostic features, but even disregarding this somewhat controversial issue, invaluable prognostic information may be gathered from the routine study of the differential formulae of the leukocytes upon frequently repeated studies through the course of the disease. Basal metabolic studies give unequivocal evidence of the activity of the process, but no diagnostic inferences may be drawn from the same. The biopsy of accessible lymph nodes frequently fixes the diagnosis and even upon suspicion should be regularly employed in this relation.

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THE INTERNIST AND THE SYPHILIS CONTROL PROGRAM

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AMONG the objectives of the American College of Physicians that have been enumerated in the articles of its Constitution are "maintaining and advancing the highest possible standards in medical education and medical practice, maintaining both the dignity and efficiency of internal medicine in its relationship to public welfare, to foster measures for the prevention of disease and for improving public health." If the College is to maintain these purposes and ideals, the fullest participation on the part of the membership is required in the current program for the control of syphilis, for this is the major public health effort of this decade.

The first paper in the first number of the first volume of the ANNALS OF MEDICINE (the precursor of our ANNALS OF INTERNAL MEDICINE) contains the following statement: "The exponent of internal medicine must know syphilis in all of its manifestations and its results. For its widespread incidence must always be taken into account as modifying disease or dominating therapy throughout the whole field of internal medicine." Thus did the president of the American College of Physicians in 1920, Dr. Reynold Webb Wilcox, in an address defining the range and scope of internal medicine, lay claim to the disease, syphilis, as rightly belonging in the domain of the internist. I suspect that Dr. Wilcox was moved to make these remarks because of the neglect of the disease by his colleagues and because he had witnessed the tendency on the part of urologists and dermatologists to seclude it in the field of their activities. His remarks may have been intended to constitute protest. However this may be, I am sure we can agree that it was then and is now a most desirable thing that medical men exhibit a keen interest in this infection. Lay and professional concern regarding syphilis is mounting steadily. It is therefore, proper that the internist look critically at the problem as it affects his practice and the public health, admitting, insisting upon, a share in the responsibility for preventing, diagnosing, treating and, when possible, curing this malady.

Those most interested in the syphilis control program expect much of the members of this College. It is felt that the position of the internist in his community is such that he will be peculiarly effective in encouraging professional and lay education, in engendering an enlightened, aggressive attitude toward the syphilis problem, in stripping it of prejudices and taboos in order that scientific medicine may better realize its possibilities. Are internists really in a position to play so important a rôle in the program? An affirmative answer is inescapable. The internist's training is such that

* Read at the St. Louis meeting of the American College of Physicians, April 21, 1937.
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he understands the significance of the term "generalized infection" and is cognizant of understood and obscure factors which operate in infectious disease. The patient and, alas, often the urologist and dermatologist may be seriously concerned in acute syphilis only with a genital ulcer or an exanthematous eruption. The internist recognizes that long before these lesions have made their appearance, the virus of syphilis is widespread throughout the body. Of tremendous importance from the standpoint of spread of disease and, therefore of the public health, the superficial early lesions have no more clinical significance in the patient's health than the localized, granulomatous ulcer marking the site of entrance of *B. tularensis* in tularemia or the rose spots scattered on the skin of the abdomen in typhoid fever. The internist knows from sad experience that the immediate threat of acute syphilis is not directed against the patient's health but against his or her contacts (the public health),—that the ultimate threat is against the cardiovascular and central nervous systems. Because he is familiar with chronic disease the internist can appreciate the significance of the term "latent syphilis" with its sinister implication that latency may be followed by activity. Furthermore the disciplines which the internist has experienced render him respectful of learning and eager for guidance when the latter is authoritative and based on scientific study and accomplishment. Data dealing with the relative value of various methods of diagnosing and treating syphilis have been accumulated. Now one can say that there are proper and improper methods. Facts have supplanted opinions regarding many treatment problems. There is irrefutable evidence that these facts are not being utilized by the majority of physicians treating syphilis. The internist appreciates the gravity of the implications of this statement, for he encounters the results of poor treatment in patients with cardiovascular, central nervous system and congenital syphilis. It is high time that he interest himself not so much with discouraging studies relative to this or that method of treating syphilitic aortitis, syphilitic hepatic cirrhosis, tabes and paresis, but with the application of his knowledge and skill to the prevention of these often irreversible, lethal conditions. This he can do if he will accept as his own the problems of preventing and treating acute and latent syphilis.

Is it worthwhile? Is syphilis so important after all? "The high incidence of known cases seeking treatment, the ratio of early syphilitic patients under treatment to the exposed contacts infected (for two individuals with early syphilis who seek treatment there are three exposed contacts infected) and the accumulating number of untreated or inadequately treated individuals with syphilis are the basis for the estimate that one out of ten adults in the United States today has or has had syphilis"¹ "A half million people acquire syphilis each year in the United States or one and one half times as many as acquire tuberculosis"²

It is estimated that there are at least 25,000 fetal deaths from syphilis

in the United States each year - It is believed that 40,000 deaths from cardiovascular syphilis occur annually. Vonderlehr has estimated that each death represents a loss of from 19 to 23 years of life with the result that the total loss from cardiovascular syphilis is from 800,000 to 850,000 years of life annually. There is a minimum of 4,500 deaths per year from paresis and 1,100 from tabes. "Since each death from paresis represents a loss of about 22 years of life and each death from tabes a loss of about 14 years of life," Vonderlehr estimates that the total loss from these two conditions is about 100,000 years of life annually in the United States. Thus it is seen that the United States population loses well over 900,000 years of life annually from cardiovascular syphilis, tabes, and paresis. The cost of the disease is apparent in terms of morbidity and mortality. The cost in dollars and cents to taxpayers, philanthropic boards, and private patients for institutionalizing for many years the physical derelicts of the disease is formidable. I shall not attempt a consideration of it. Suffice it to say that the cost is obviously far greater than for any plan for control, however expensive the latter may be.

Is it feasible to attack the problem? What weapons have we, and are they effective? The etiology of the disease is known. We have accurate tests for its presence. The diagnosis, in cases which can be effectively treated with present methods, is not difficult. Treatment, though far from ideal, is effective, if properly applied, in (a) curing and rendering non-infectious the vast majority of patients with early syphilis, (b) in preventing congenital syphilis, (c) in protecting patients with latent syphilis from the sequelae of chronic infection, and (d) in prolonging life and comfort in the established, chronic disease. If our present knowledge were utilized to its fullest, the disease could be promptly brought under control. To this end, a program, sponsored by the United States Public Health Service under the leadership of Surgeon-General Thomas Parran, has been formulated. This program involves education of profession and public as to both the menace of the disease and the possibilities of its control, the improvement of facilities for the care of patients of all economic groups, the development of a public health attitude toward the disease with special emphasis on case finding through contact studies, rendering patients with acute syphilis non-infectious by proper treatment, curing, when possible, and preventing congenital syphilis. To this end the practitioners of the country, who care for over half of the syphilis which is recognized and under treatment,³ and the public health forces are being organized for the attack. Is it not fitting that we consider and establish our position, as internists, in this undertaking?

The first and most effective thing that the individual internist can do to contribute to the success of this control program is to familiarize himself with modern concepts of diagnosis and management of the disease—to learn and practice sound medicine in so far as syphilis is concerned. No more important step could be taken toward the successful consummation of this

program than that the internists of the country give syphilis its proper place in their discussions, thought and practice. How many internists are actually mindful of the following facts relative to syphilis: that it is a generalized infectious disease long before the appearance of skin and mucous membrane lesions, that the acute stage of the disease is a critical period in the life of any syphilitic from the viewpoint of the public health since it is the time that he or she infects others, that the early acute phase of the infection is the time during which the spirochetes are disseminated throughout the body, and that it is the time of the laying of foundations for the later development of cardiovascular and central nervous system disease, and, finally, that the acute disease is clinically curable.

Are these important facts known to all internists and, if they are, are all internists duly impressed with the great opportunity for prevention and cure that each patient with acute syphilis presents? Is it common knowledge that the present standardized methods of treatment for acute syphilis, involving scheduled treatments for well over a year, are greatly superior to other treatment plans and that the patient's chance for cure is dependent upon such management? ¹ Do all good physicians use these methods? Does every patient with acute syphilis raise a question in the doctor's mind as to the existence of unrecognized contact infection? Does he try to find the source of his patient's disease and render it non-infectious? Does he think of syphilis and its threat whenever he sees a pregnant woman and does he insist upon a serological test for its presence or absence? The answer to most of these questions is in the negative. The medical profession in general, including internists, must admit to an attitude of casualness and indifference with regard to syphilis, which is, to say the least, inconsistent with medical traditions and ideals.

What, to be specific, should the intelligent internist know and do? What are the "minimum requirements" with regard to attitudes and practice?

First, know and teach that syphilis is highly infectious during its acute phase and that for every case of acute syphilis there is a source and that this source spreads disease.

Second, know and teach that the foundations for serious, late manifestations of syphilis are laid in the early stage of the infection.

Third, know that the acute stage is the important stage to treat—both from the public health point of view and also from the point of view of the patient's future health. Here is the golden opportunity to practice both preventive and curative medicine.

Fourth, remember that even after the golden opportunity has passed, congenital syphilis can be prevented and many of the sequelae of syphilis can be forestalled by adequately treating latent or chronic syphilis.

We shall see in this generation a marked reduction in the incidence of acute syphilis in the United States. Many of us will live long enough to witness a reduction in the incidence of congenital syphilis, neuro-syphilis,

cardiovascular and visceral syphilis. Bereft of its age-old prejudices and taboos the syphilis problem is being presented to the medical profession and to the public. Means to cope with and to solve this problem are at hand. They are admittedly not ideal but they are, nevertheless, effective. Failure of the current program could be attributed only to lack of intelligent co-operation on the part of all parties involved—a most important group being, for reasons which I have indicated, the internists.

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PROGNOSIS IN TUBERCULOSIS¹

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INTRODUCTORY

WHEN one considers the prognosis of tuberculosis in its widest implications he is obliged to extend his discussion to every phase of the tuberculosis problem and consider every factor which influences bacillary growth and activity or modifies individual resistance. The outcome of the disease is influenced by the virulence and numbers of infecting bacilli, the type of the disease and its severity, the constitutional peculiarities of the patient, his general reacting powers, his condition at the time when infection occurs, the character of the tissues which are involved, the nature of the lesion, the time when the diagnosis is made, the character of treatment and when it is instituted, the age, economic and social status and intelligence of the patient, the character of the climate and weather to which the patient is exposed, the psychology of the patient and of the friends who advise him, the physician who carries out the treatment, his psychology as well as medical knowledge and experience in meeting the problems of the tuberculous patient, the place where the treatment is to be carried out whether at home, in a sanatorium or in a dispensary, and many other factors of greater or lesser import.

It is not always the big thing that determines the outcome in tuberculosis. We at times see the prognosis changed from favorable to unfavorable and the reverse as a result of some very small factor which might, under ordinary conditions, seem of minor importance.

In the time allotted to this paper I shall confine myself largely to the influence which a competent physiologic reaction and a competent compensating mechanism on the part of the patient has upon the prognosis of tuberculosis, and further point out the difference in a prognosis from the standpoint of healing and from the standpoint of physical efficiency.

TWO BASIC FACTORS ON WHICH PROGNOSIS DEPENDS

The healing of tuberculosis is a physiologic process, and, when the physiologic balance of the patient is good, tuberculosis shows a strong tendency to heal. That the prognosis is favorable, provided the disease is treated intelligently in its early stages, is now generally acknowledged, because the patient's resisting power is good and the ability of the lung tissue and thoracic cage to compensate for the loss which results from infiltration cavity or fibrosis is excellent. When these early cases fail to heal it is usually due to the fact that conditions necessary to the healing process were

* Read at the St. Louis meeting of the American College of Physicians, April 20, 1937

not established. That the prognosis is less favorable in the far advanced stages and when improperly treated in all stages is equally well established.

With the well established forms of treatment everywhere recognized today, there are few places in civilized countries where a patient suffering from tuberculosis can not be given a fair chance of recovery if aid is sought at a time when the disease is curable. This is very different from what it was a quarter of a century ago, for even so recently as that, well trained specialists were few, the general opinion of physicians was that the disease was hopeless, and the aid necessary to cure was rarely to be had.

The two most potent factors in changing the prognosis of tuberculosis in recent years from the status of an all time hopeless disease to that of one that is curable have been the large group of medical men who have made tuberculosis their special study, and the systematic spread of knowledge concerning the nature of the disease by interested workers. It is almost an unbelievable fact that this change in prognosis has come within a single generation.

NEXT STEP IN IMPROVING PROGNOSIS

Probably the next greatest advance in prognosis will be brought about by the medical profession considering tuberculosis in the same category as other diseases. General medical men should understand tuberculosis and show the same interest in it that they show toward diseases of the heart, kidney and gastrointestinal tract, or diabetes or blood diseases. When they do this we may hope not only for an earlier recognition than today, but also for the application of treatment when it will be more effective. In no disease can a physician render a greater service to a patient or to his family than in making an early diagnosis of tuberculosis and directing him so that he at once receives adequate treatment and at once minimizes the danger of infecting others. It not only means saving the patient's life and restoring him to usefulness, but saving others who associate with him from infection. The importance of instituting immediate treatment is particularly emphasized by the fact that the disease so often affects the bread-winner and is so often found in the years of early adult life when the domestic, economic, social and cultural interests of the family depend upon the patient's ability to carry on with as little loss of time and efficiency as possible.

PROGNOSIS AS IT RELATES TO IMMUNOLOGIC REACTION

In order to make an intelligent prognosis we must understand something of the intimate reactions which make up the defense mechanism of the patient, for these are basic in prognosis. They vary greatly in different individuals. Tuberculosis is a chronic inflammatory disease. The accompanying inflammation is due to the reaction between bacilli and their products on the one hand, and the tissues of the patient on the other. The reaction, being inflammatory, carries with it local irritation of cells, dilata-

tion of blood vessels, and an exudation in the tissue spaces with an increased serum and cellular content at the site of the injury, all of which belongs to the defense reaction.

Both bacilli and tissue cells may be destroyed as a result of the conflict which goes on for mastery. As a result of the irritation and destruction of tissue cells, enzymes are set free which produce bacteriolysis. Destruction of bacilli is further carried on by cells which possess phagocytic qualities. Resulting both from the growth and the destruction of bacilli, substances are set free into the tissues which gain access to the circulation and stimulate the defensive function of cells throughout the body. Thereafter, when bacilli or bacillary substances gain entrance to the tissues they are anchored and destroyed with increased avidity.

Local defense takes upon itself two forms, one that of bacteriolysis, the other that of tubercle formation, the one primarily destructive of bacilli, the other primarily fixative in that it tends to hold them in situ.

General defense, on the other hand, consists in establishing an increased power on the part of the tissues generally for opposing both bacilli and bacillary products. While certain cells normally have greater defensive powers than others, it seems that every cell of the body is endowed with the function of defense and that it is stimulated to unusual proportions as a result of infection. We call this increased defense immunity. This increased physiologic reaction is the factor which makes it possible for the organism to oppose successfully millions of bacilli in advanced extensive tuberculosis, although first infection may have been brought about by a very few.

While the defense strategy of the body, in case of an attack of microorganisms, consists in concentrating its most effective forces at the point of invasion it carries out the principle of universal conscription and arms all cells so as to guard every area of the body from attack while continuously sending up new forces to the front so as always to have fresh troops guarding the most exposed areas.

In order to understand how prognosis may be modified by the general condition of the patient it is necessary to understand that specific defense is a quickened and heightened response of a physiologic function normally possessed by the body cells, and, that this function is just as normal as that which produces secretions having special properties or that which produces muscular action. So, warding off infection, destruction of invading microorganisms, and the repair of the injury which has been caused are all physiologic processes, the competency of which depends much upon the condition of the patient.

The body's defense is sufficient as a rule to either wholly destroy the few bacilli which enter the tissues at the time of first invasion, or, to hold them largely fixed at the point of entry and in the lymph glands which drain the infected area. But the fact that infection is established is evidence that the numbers of bacilli are greater than the local cells, with their normal

protective function, are able to cope with, and, furthermore, it is evidence that unless this protective power can be increased the infection cannot be successfully opposed. The general principle in physiology of increased response to unusual stimulation now quickly comes into play, and within a few days after bacilli have become implanted in the tissues all cells of the body are able to put up an augmented defense. If tuberculosis extends thereafter, it does so against increased opposition which tends to restrict the extent and severity of the metastases. The prognosis in the more simple lesions which succeed the primary complex is determined very largely by the degree of competency of this protective mechanism.

Tuberculous infection, opposed by increased cellular defense, results in the so-called "adult type of infection." In the adult type, on account of this increased cellular defense, the lymphatic route of spread which was open and free to bacilli at the time of first infection is now largely closed, shutting off the easiest route for bacilli to follow in spreading throughout the body. Bacilli which enter the tissues by way of the blood and canalicular routes such as the bronchi now also meet with increased opposition to implantation and are often destroyed without producing infection, or, if infection is established, it often becomes abortive. This protection in the previously infected individual is so efficient that, unless the numbers of infecting bacilli be great, there is little danger of permanent metastases forming in the early stages of the disease provided, of course, the patient is put at bed rest and so treated as to maintain a normal physiologic response. The increased local and general physiologic responses of the body, if only the patient is maintained in a state of high physical fitness, make the prognosis in early clinical tuberculosis almost invariably favorable.

PROGNOSTIC SIGNIFICANCE OF CASEATION

While the major pathologic processes may be described as predominantly exudative and predominantly proliferative, the most serious phenomenon which is met in the pathology of tuberculosis, the one which carries with it the possibility of affecting prognosis most unfavorably, is caseation and softening, because this process is responsible for cavity formation and furnishes the source of bacilli which produce metastases by spreading through such natural channels as the bronchi.

A patient may be incapacitated by the gradual encroachment which a preponderantly proliferative lesion makes upon his reserve pulmonary tissue, but sooner or later caseation with destruction of tissue and cavity formation will usually accompany and increase such incapacity. It is caused by a violent protective reaction of immunized tissues against an unusual number of infecting bacilli or large quantities of their protein products. Multiple cavity can be largely prevented by the immediate application of adequate treatment while the disease is early.

Caseation often takes place early in exudative infections because the tis-

sues are in a state of hyperergy. The anchoring ability of the cells is so great that the protein is fixed in such large quantities that it obstructs the capillaries, cuts off the blood supply to the tissues, and causes them to caseate and undergo destruction, but as the tissues become more accustomed to the infection it seems that the degree of protection becomes greater while the cellular reaction becomes less violent. This is of great prognostic significance, for either a degree of desensitization of the cells takes place or the protein is prevented in some other manner from producing severe localized reactions. While cavity often accompanies an early exudative lesion, a second one rarely follows immediately thereafter, even though the infection continues to spread, and furthermore, few relatively large cavities appear during the course of chronic proliferative lesions except as a result of the fusion of smaller ones. This highly protective mechanism can be relied upon as being the greatest factor in the healing of tuberculosis. Even the extent of destruction may be kept to a minimum by taking advantage of it by the modern methods of treatment which limit the danger of metastases forming by keeping the patient in a state of high physiologic balance. This may be accomplished by the application of rest and other proper physiologic therapeutic measures immediately on the infection assuming clinical importance.

Even a large cavity, today, is far from being the hopeless phenomenon that we formerly thought. The early freshly formed cavity, unless it be situated unfavorably, will usually heal spontaneously, if the patient's reacting powers are quickly brought to a state of efficient action, for the pulmonary tissues are able at this time to take on emphysematous change, and the bony thorax is able to reduce in size and lessen its movement, and these together bring about the conditions required for healing. However, unless cavity is treated properly, it reacts very unfavorably upon prognosis, for it reduces the chances of healing and furnishes an open focus from which bacilli can readily spread and form other metastases.

PROGNOSIS IMPROVED BY ARTIFICIAL COMPENSATORY MEASURES

Up to the present time most patients who have been treated for tuberculosis have been treated after the disease has become advanced. In these cases both the physiologic balance of the patient is severely disturbed and the mechanism by which compensation takes place between the lung volume and thoracic cage has already been utilized to its limit. So physicians have spent their energy attempting to overcome the many discouraging conditions which this chronic infection presents. However, they have been unwilling to accept defeat and by their ingenuity have devised measures with which to cope with many of the mechanical conditions which adversely influence the prognosis in these cases. The physiologic factor, too, is gradually becoming better understood, but there still is no way of restoring the function of exhausted cells. In healing tuberculosis, nature lessens respiratory move-

ment and reduces the size of the thoracic cage to adjust to the volume of pulmonary tissues as it is reduced by the disease. The tissues adjoining infiltrations in the lung also adjust by becoming emphysematous and enlarging, thus relaxing and compressing the infiltrated and excavated tissues.

Experience has shown that these results may be attained artificially by utilizing relaxing and compressing measures, such as weights upon the chest wall, pneumothorax, pneumoperitoneum, paralysis of the diaphragm and thoracoplasty. These measures promote healing mechanically by reducing respiratory movement, relieving diseased pulmonary tissues of tension, and compressing them. In many cases of advanced tuberculosis these measures bring about favorable mechanical conditions without which a physiologic balance, no matter how stable, would be unable to produce healing. However, no matter how frequently healing follows, it must be understood that the protective and reparative processes depend upon the patient's physiologic response.

PROGNOSIS FOR HEALING AND EFFICIENCY DIFFERS

Through relaxing and compressing measures the prognosis in many cases of severe and serious tuberculosis has now become fairly favorable from the standpoint of bringing the disease to a state of quiescence or arrest. This is truly a great accomplishment, but it is still unsatisfactory in that it too often restores a mechanism, which has been injured by neglect, to a limited capacity when our knowledge and understanding of the problems involved warrant a restoration to full capacity. Any measure that carries with it an avoidable reduction in the patient's future efficiency, no matter if the tuberculous process is healed, has in it elements of defeat which medicine must overcome.

To make my meaning clear it is only necessary to contrast the health and full efficiency which a patient suffering from an early limited lesion usually secures through treatment, with the handicap of limited efficiency and insecurity which he usually obtains through the most effective treatment possible when the lesion is far advanced. When we see the interference with the mechanics of respiration, the reduction in lung volume, and the resultant inability to compensate and measure up to the calls for extra physical exertion which is a common occurrence following the best result that can be attained in many far advanced cases of tuberculosis, we should be led to bend every energy towards securing treatment at a stage when such handicaps would rarely follow.

DISCUSSION

From the preceding discussion it may be established that in combating tuberculous infection and in promoting healing we are dealing with functions with which the patient is normally endowed. If cure is accomplished, the patient accomplishes it through these normal functions. If we, as physi-

cians, improve the prognosis, we do it by increasing the patient's own powers and facilities, not by adding something new and extraneous. If only we bear in mind that the phenomena which we meet in the tuberculous process, the proliferation, the exudation and the necrosis, are intimately connected with the immunologic and healing processes, which in turn depend upon the physiologic mechanism of the patient, we will be able to make a more accurate prognosis.

In regard to prognosis it can be said that with stable physiologic equilibrium and favorable conditions for compensatory adjustment on the part of an individual, a limited infection produced by a relatively large number of bacilli, or a smaller number of relatively virulent bacilli, may readily heal, and an infection which may occur at a time when the host's physiologic equilibrium is temporarily lowered may be healed by restoring his physiologic processes to normal, but, should an infection be large or the bacilli be extra virulent, or should the host's physiologic processes remain in a condition of instability for too long a time, then healing of the process may not only fail to take place but metastases may form creating other foci of infection, and from these further metastases may take place, repeating the cycle until healing may become impossible.

While mildly reacting limited lesions are comparatively easy to overcome, multiple or extensive lesions produce a proportionately greater disturbance in the host's physiologic and compensatory processes and bring about a relatively greater tax on his defensive and healing powers. So an advanced and advancing process reduces the favorableness of prognosis by presenting greater difficulties to be overcome before healing may be accomplished, and by causing the host's protective and healing mechanism to be rendered less effective for its task. It is self-evident, then, that the favorableness of prognosis steadily decreases as the tuberculous infection extends quantitatively and as the pathologic changes advance in severity. It is likewise self-evident that a rapid restoration of the patient's physiologic functions, among which is that of defense against infection, greatly improves the prognosis in any case.

Theoretically, one should have little fear but that a normal physiologic function on the part of an individual with a limited tuberculous infection would be able to bring about healing provided it is maintained long enough, and this has been proved by many years of experience. Theoretically, one should expect that the more advanced the process quantitatively and qualitatively the greater the difficulty in securing a healing and the less efficient the patient would be thereafter, and, the experience of many years has shown this to be true. Theoretically, advanced tuberculosis with destructive lesions should be difficult and often impossible to heal by any possible restoration of physiologic balance, and many years of experience have also shown this to be true.

The prognosis in tuberculosis is modified by the character of the lesion,

which depends very much upon the individual patient and his particular physiologic reaction. It furthermore is plain that these two factors are largely in the hands of the physician, to be modified through the application of therapeutic measures. Whether the disease will spread or the patient will be able to defend himself successfully against it depends very much upon the treatment which is carried out. Since healing is primarily physiologic this places the burden of prognosis largely upon the physician, for he determines whether or not a proper physiologic balance is established and maintained.

Before the necessity of maintaining an equilibrium between the size of the thoracic space and the lung volume was understood as being a prime factor in prognosis, pneumothorax and other measures of relaxing and compressing the pulmonary tissues were established, and it was thought that their main purpose was compression or enforced rest to the lung. While this is often true in far advanced cases, it is hardly so in those early cases which will heal spontaneously under hygienic measures alone. Compensation in these cases is necessary rather than active compression.

It is generally accepted that pneumothorax has improved prognosis more than any other measure used in treatment. There is no doubt that it reduces the danger of spreading, that it improves the chances of certain advanced cases that were found to be incurable by older methods, and that it gives the physician a control over the patient. It will not only produce favorable results in a very large group of comparatively early cases, but also in another group that rarely heals without some form of artificial aid. This, particularly, is what has made it so popular, for most cases under treatment belong to this class. However, let us not deceive ourselves, for the best prognosis, with or without compression, is found in early cases.

If we were to discuss the manner in which prognosis is influenced by various procedures, we should divide the patients into those in whom artificial compression measures are necessary and those in whom they are not. As it is now, credit is given to compression measures in many instances in which the lesions would have probably healed under hygienic measures alone. Those early cases in which the patient is able to make his own compensation, if collapsed, add to the prestige of pneumothorax, when in reality a similar result could have been obtained without it.

Pneumothorax has become exceedingly popular in instances in which adequate medical supervision cannot be had. The great majority of tuberculous patients are treated in public institutions in which the number of beds is inadequate and the medical service is undermanned. Therefore, it has become necessary to meet the problems with the facilities which are at hand. To do this compression therapy has been used, not so much because it is necessary for healing, but as a matter of expediency in order to make the facilities meet the needs of the community. Early cases in which the question of healing under hygienic measures is hardly questioned are submitted to

compression therapy, the purpose of which is to render patients bacillus-free as quickly as possible and send them back to their homes, leaving the beds in the institution for others

All of the early cases that are collapsed in this way add to the prestige of collapse therapy. The effect is to brand the prognosis in most cases of tuberculosis as unfavorable unless collapse therapy is used. That such an attitude is wrong may be shown by the statistics of institutions which treated tuberculosis before artificial compression was generally used. How wrong it is cannot be determined until statistics covering many cases treated with and without pneumothorax are analyzed in an unbiased manner. Recent studies from English sanatoria show better results without operative measures while those from Detroit show best results with

Admitting that artificial compression, particularly pneumothorax, will enable us to secure a healing in many patients in whom we would fail otherwise, let us not forget that rest with spontaneous compensation or spontaneous compensation supplemented by temporary phrenic interruption will bring about healing in a very large percentage of the early cases and restore the patient to health with a minimum degree of physical inefficiency, produced either by the disease or as a result of the therapy. Pneumothorax produces injury to the respiratory mechanism of the patient in quite a number of instances, and in discussing prognosis all such injuries must be considered. Thoracoplasty, which is a boon to the patient who faces the alternative of healing with incapacity of one lung or of remaining ill, cannot be defended as a desirable treatment. It is the treatment that all would like to escape if possible, but the years of life and comfort it adds are a blessing to the one who cannot do better. We hope, however, that its necessity will become less and less as the truths about tuberculosis become more generally disseminated.

Tuberculosis specialists should urge early diagnosis and immediate restoration of physiologic balance as one of the most important factors in improving the prognosis of this disease. No one would take from far advanced cases the opportunity of healing, even though they are seriously handicapped during the rest of their lives, but the fact that these patients with advanced disease can be handled successfully from the standpoint of cure must not blind one to the unnecessary loss of efficiency that is brought about by treating cases which are far advanced instead of early.

The improvement in prognosis which has been brought about by scientific ingenuity should be accepted for what has been accomplished, but it should not satisfy medical men if better results are possible. On the contrary, it should stimulate humanitarian sentiments so that every tuberculosis worker would proclaim long and loud, in season and out of season, that lives and efficiency are needlessly sacrificed by allowing clinical tuberculosis to extend beyond the time when its cure can be brought about in most instances through the stimulation of normal physiologic functions and through na-

ture's own compensatory mechanism, 'or at most by the use of the simpler operative measures

SUMMARY

The cure of tuberculosis is accomplished through normal physiologic processes. The lung may be reduced in volume by infiltration, cavity and fibrosis, and the adjustment of lung volume to the size of the thoracic cage is important in healing. In advanced cases healing may be prevented unless such compensation can be made. The prognosis, then, depends upon physiologic competency and compensatory adjustment.

The prognosis for healing and for efficiency differs. The prognosis in tuberculosis in its early stages is favorable for healing, and also for the future efficiency of the patient. The prognosis in far advanced cases, with the newer methods of treatment, is quite favorable for healing, but the prognosis for efficiency is lowered.

The profession should not be satisfied with the present status of therapy. Too many patients come under treatment only when the lesions are of such severity that the measures required to produce healing are so radical as to entail a lamentable reduction in the patients' future respiratory efficiency.

In order that patients may be treated during the favorable stage of the disease, the medical profession should take the same interest in tuberculosis as it does in other diseases, prepare itself for making early diagnoses and understand the principles of therapy, so that proper treatment may be immediately applied.

SCARLET FEVER¹

By JEAN V COOKE, M D , *St Louis, Missouri*

THE modern conception of scarlet fever may be summarized briefly as follows

The evidence that scarlet fever is caused by hemolytic streptococcus infection is convincing and this etiology of the disease is generally accepted as proved. The constant association of the clinical disease with some focus infected with these organisms, the production of experimental scarlet fever by purposeful inoculation of susceptible volunteers with cultures of streptococci, and the various biologic reactions produced by injection of hemolytic streptococcus filtrates leave little room for doubt that the hemolytic streptococcus is the essential cause of the disease. As a result of observations on scarlet fever as a streptococcus infection, it has become evident that the disease is a composite one and that the manifestations can be separated into two distinct groups. The first group includes those phenomena resulting directly from infection and invasion of the tissues by the streptococcus and constitutes the *septic* component of scarlet fever. These septic manifestations are clinically identical with those of similar nonscarlatinal pyogenic infection and include the acute pharyngitis of varying degree seen in the usual form of scarlatina, as well as the localized infection of the skin or endometrium noted in the surgical or puerperal types, the direct extension of the infection to adjacent tissues in such complications as otitis, mastoiditis, cervical adenitis, or phlegmonous angina, and the accompanying malaise, fever, and leukocytosis common to acute streptococcus infections of this character. The second or *toxic* component of scarlet fever includes those added manifestations which are caused by the absorption of specific toxic substances derived from the streptococci themselves. All of these can be reproduced in susceptible persons by the injection of sterile streptococcus filtrate and are obviously quite distinct from the changes produced by direct tissue invasion by the organisms. The purely toxic phenomena include the rash with the accompanying enanthem, the initial vomiting, slight general adenopathy, fever, and, in addition, the less constant manifestations of arthritis and hematuria. Although the toxic phase is combined with the septic in clinical scarlet fever, the two processes are immunologically separate. Certain persons, for example, who are immune to the toxic action of absorbed bacterial substances, may suffer severely from scarlatinal streptococcus infection—the *scarlatina sine exanthemate*—and in many fatal cases of the disease death occurs from the septic infection after the specific toxic symptoms have disap-

¹ Presented at the St. Louis meeting of the American College of Physicians, April 21, 1937.

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peared. Conversely, it has been noted not infrequently that certain children with marked skin sensitivity to the streptococcus filtrate fail to develop scarlet fever after exposure. This again shows the lack of a constant relationship between susceptibility to the toxic phenomena and immunity to streptococcus infection. Those persons, for example, whose cells are very susceptible to the action of streptococcus products, may possess a well-defined tissue immunity to streptococcus infection. Such protection from scarlet fever is probably dependent on local tissue resistance to infection rather than on circulating antibodies.

The relative seriousness of the effects of these two distinct components of scarlet fever is of some interest. In general the septic element of the infection is by far the more important part of the disease. All serious and fatal complications which are observed appear directly attributable to the invasion and extension of the streptococcus infection. While the specific toxic symptoms are clinically more striking and obvious, they are of relatively short duration, in the majority of cases of a mild character, and have usually disappeared by the time any serious septic complications occur. Those very rare fulminating cases in which severe toxic symptoms are followed shortly by death have suggested that the fatal outcome could be directly attributed to the specific scarlatinal toxemia, although even in such instances death might as readily be due to the intense streptococcus inflammation.

While the exact part played by the specific toxic phase in the serious effects of scarlet fever is as yet unsettled, it is difficult to believe that it plays any but a minor rôle. Regarding the infection itself, the conditions upon which individual resistance or susceptibility to the entrance of the infecting streptococci depends and the manner by which the body overcomes the infection are very imperfectly understood and the recent investigations on scarlet fever have furnished no explanation of them. Whether the specific scarlatinal toxemia has any part in making the septic streptococcus infection more serious is still uncertain. Certainly such added specific toxemia produces a more intense clinical illness during the first week of the infection, although in general the complications and sequelae of streptococcal infections without a rash appear to be quite comparable in degree and severity with similar infections of scarlatina with typical toxic rash.

In the past 50 years the morbidity of scarlet fever has apparently increased while the mortality has decreased. The most probable explanation of this is that during this period there has been an increasing percentage of very mild infections. Whether such infections are actually acquiring a less virulent character, or whether many patients now diagnosed as scarlet fever were previously called nonscarlatinal toxic rashes it is impossible to determine, but possibly both factors play a part in the increased morbidity and decreased mortality. In recent years the mortality has varied from 0.5 per cent to 3 per cent, and the normal mortality is considered to be around 2 per cent. As with all streptococcus infections, especially when they occur in epi-

demio form, there are some years in which virulence and mortality are somewhat above the normal rate. It is important to remember such periodical variations in the virulence of epidemics, especially in interpreting the results of therapy, since certain claims for specific therapeutic measures are based on mortality variations well within normal yearly variations. To the laity the term "scarlet fever" still carries a menace to life and hearing not at all justified by the character of the disease as it exists today.

The question of the relationship of so-called nonscarlatinal streptococcus infections or those without the specific skin rash to typical clinical scarlet fever is an interesting one. It is generally accepted that when scarlet fever occurs in epidemic form, certain contacts suffering from typical streptococcus throat infections but with no rash or other specific toxic manifestations, actually have scarlet fever infection without a rash. On the other hand, when similar streptococcus throat infections occur sporadically, they are usually called merely acute tonsillitis and few consider a possible relationship between them and scarlet fever. Epidemiologically, however, the physician who treats scarlet fever finds that the majority of the patients he sees are sporadic cases and have not been in contact with another case of the disease. It has often been puzzling to understand how such a large percentage of patients with a communicable disease could acquire it without apparent exposure. It has, therefore, become increasingly evident from a purely clinical standpoint that streptococci capable of producing scarlet fever are very widely distributed. The problem of the specificity of streptococci causing scarlet fever, therefore, becomes of some importance epidemiologically, and the question of whether a certain strain of streptococcus or several strains, or indeed almost any pathogenic hemolytic streptococcus may cause scarlet fever, must be considered. The classification of these organisms and their identification and separation has been studied by two methods. First, by means of such bacteriological methods as agglutination and agglutination absorption experiments with immune serums, and second, by a comparison of their ability to produce a specific skin reactive toxin, or specific erythrogenic substance which is neutralizable by human or animal immune serums. Several workers have shown, for example, by agglutination tests with immune rabbit serums, that a very large proportion of the strains isolated from scarlet fever had similar agglutinative characteristics and could be differentiated from strains isolated from nonscarlatinal sources, such as local or general pyogenic infections. This strongly suggested that certain strains were specific for scarlet fever. On the other hand it was later shown that the streptococci isolated from early scarlet fever cases not only differed from those from other sources but also differed from those streptococci isolated from patients with scarlet fever during the third and fourth week of convalescence. Such differences suggest that the group relationships demonstrable by agglutination tests may be altered by the environmental factors in the host which change the specific agglutinability of the streptococci, and that

these differences may not be due to inherent strain differences. Eagles, for example, believes that hemolytic streptococci are a group of organisms whose specific agglutinative qualities may be altered by factors operating upon them in vivo. There is much evidence for the belief that with streptococcus infections just as with tubercle bacillus infections, the different types of clinical disease produced may depend not on variations in the strain or type of infecting organism, but on differences in the host himself. While age, portal of entry, dosage and virulence of the infecting agent are of some importance, the varying reactivities of host's tissues, such as cellular resistance, constitution, and especially previous contact with the infecting antigen, must have a large effect on the type, character and severity of the clinical manifestations.

The second method by which attempts to demonstrate specificity have been made, has been the study of the ability of any given organism to produce a scarlatinal toxin, or the specific erythrogenic substance in culture filtrates. Most streptococci isolated from scarlet fever produce such toxin, although there is a considerable variation in the amount of toxin formed by different strains. Streptococci from nonscarlatinal sources, such as middle ear and mastoid infections in infants or other suppurative lesions, and even erysipelas also produce scarlatinal toxin in a large percentage of cases, and different organisms show a similar variation in titer of toxin. Occasionally strains from nonscarlatinal sources are far more potent in producing it than scarlatinal strains. This toxin from nonscarlatinal sources cannot be distinguished from scarlet fever toxin, since it is neutralized by scarlatinal antitoxin and immunization of Dick positive children by it is followed by the development of negative Dick tests to scarlatinal toxin. As further evidence of the similarity between the toxin produced by streptococci of scarlatinal and of nonscarlatinal origin may be mentioned the effect of various types of streptococcus anti-serums on acute scarlet fever. Many if not all varieties of commercial anti-streptococcus immune serums, such as anti-erysipelas serum and polyvalent anti-streptococcus serum, have the same effect in causing a fairly prompt fading of the rash and other toxic symptoms when administered early in scarlet fever, as does the scarlatinal antitoxin made from strains of scarlatinal origin. It is possible, for example, to produce a Schultz-Charlton local extinction test or local blanching of an early scarlatinal rash by the intradermal injection of 0.001 c.c. of certain commercial anti-erysipelas serums. Since such serums are produced from strains other than those from scarlet fever, it seems evident that nonscarlatinal strains contain the so-called specific erythrogenic toxin with considerable frequency.

From such observations as have been briefly summarized it would seem that there is little evidence that scarlet fever streptococci possess a specificity that distinguishes them from other streptococci, that the potentialities of any streptococcus to cause scarlet fever must depend largely upon its ability to produce the erythrogenic toxin to which patients with clinical scarlet fever are susceptible, that a large percentage of streptococci from scarlatinal and

nonscarlatinal sources can form this toxin, although there is some variation in the amount produced, and, finally, that if all strains of streptococci cannot secrete toxin in sufficient amount to cause the toxic symptoms in susceptible persons after infection, certainly the dissemination of streptococci capable of producing the clinical disease is so widespread that one may well consider any open streptococcus infection as a potential source of scarlet fever. In general, if the infection occurs in a person immune to the toxin because of the presence of specific antibody in his blood, the diagnosis is non-scarlatinal streptococcus disease, whereas if it occurs in a person susceptible to the toxin, the disease is called scarlet fever.

The inconsistencies of this attitude are apparent and there is an increasing tendency among many to doubt whether scarlet fever is to be any longer considered as a distinct disease entity. It seems likely that clinical scarlet fever is merely a toxic syndrome that accompanies hemolytic streptococcus infections in certain susceptible persons and it would be more consistent to consider it a scarlatinal type of streptococcus infection or a streptococcus infection with scarlatinal toxic reaction.

It has been mentioned that in the majority of cases of scarlet fever infection, the specific toxic symptoms are mild and no attempt at specific therapy appears warranted. In certain patients the toxicity is severe and in these, the injection of serum antitoxin produces a fairly prompt and often striking beneficial effect on the rash and other toxic symptoms. Such an effect, however, is obtained only if the serum is given in the first three days after the rash appears, and if serum is administered later when the toxic symptoms have reached their height, no beneficial results are observed. Serum treatment, even though given early, appears to have little or no effect upon the septic manifestations or on the streptococcus local infection. Frequently patients have been observed in whom early serum treatment produced a prompt and apparently complete cure of the specific toxic phenomena, but later the septic streptococcus disease spread alarmingly and in certain instances was fatal. Indeed as previously cited, practically all dangerous manifestations are attributable to the septic component of the disease and occur or persist after the specific toxemic symptoms have disappeared. The chief function of serum treatment appears to be symptomatic and directed primarily at controlling the toxic symptoms. When these symptoms are mild, the use of serum is not indicated. A striking disadvantage of routine use of serum in such mild cases is the frequency with which various types of serum reactions occur, some of them causing considerably more distress than the scarlet fever itself. There is little evidence that serum treatment affects the ultimate outcome of the infection.

Although it would appear that the specific toxic factor and the specific toxemia play a far less important and serious part in scarlet fever than the septic streptococcus infection, the character of the toxemia and the mechanism of its production are of much interest. There are two main hypotheses

which have been advanced to explain the production of scarlatinal toxemia. These hypotheses are quite different and a belief in one or the other of them alters considerably one's conception of the mechanism of scarlet fever, and one's procedure in attempting to control it. They may be termed the *toxin hypothesis* which assumes that the toxic agent is a primary streptococcus bacterial exotoxin analogous to other such familiar toxins, and the *allergic hypothesis* which asserts that the streptococcus product producing the symptoms is not primarily toxic and that its toxic action is due to an acquired hypersensitivity of the host's cells from previous streptococcus infection. Before speaking of the evidence supporting these hypotheses, these two types of poisons may be briefly defined so that the distinction between them may be more apparent. A true toxin is a substance which poisons or injures normal cells unless such cells are protected by the presence of a specific neutralizing antibody or antitoxin, which is a cellular product resulting from previous contact with the same toxin. An allergen, on the other hand, has no poisonous action on normal cells unless such cells do have a specific antibody which is a product resulting from previous contact with the same allergen or antigen. With a true toxin the specific antibody, therefore, protects the cells from toxic injury, while with an allergen the specific antibody renders the cells susceptible to toxic injury.

The chief observations upon which the toxin hypothesis is based are as follows:

- 1 The production of characteristic toxic symptoms by the injection of the filtrate into susceptible persons.

- 2 The appearance of a local area of erythema (Dick reaction) in the skin of susceptible persons after the intradermal injection of filtrate.

- 3 The presence of a neutralizing antibody in the blood of convalescent scarlet fever patients, of many persons with negative Dick reactions, and also of filtrate-immunized animals. This antibody resembles an antitoxin since (a) when the toxic filtrate is mixed with serum containing the antibody, the filtrate will no longer produce a positive Dick reaction on the skin of a susceptible person, (b) when the serum is injected intradermally in an early scarlet fever rash, a local blanching of the eruption occurs after a few hours, and (c) intramuscular injection of serum in early scarlet fever cases frequently causes a relatively prompt disappearance of the specific toxic symptoms.

- 4 By the injection of filtrate into persons with positive Dick reactions, using small quantities at first, followed by gradually increasing doses, the Dick reaction becomes negative, and after some weeks the specific neutralizing antibody appears in the blood.

It is apparent from the foregoing characteristics that, under certain conditions, the filtrate is toxic for man and that it stimulates the production of neutralizing antibody. In these respects, the analogy to a true bacterial exotoxin is close. However, in certain other respects the biologic reactions

and properties of the filtrate differ considerably from known soluble toxins. For example, the specific toxicity of the filtrate is limited to human beings, and in animals no toxic symptoms are produced by its injection, in spite of the fact that animal blood contains no neutralizing antibody. Young infants, also, show no toxic effect from the filtrate and have negative skin tests, even though they are unprotected by the specific antibody. Apparently, susceptibility to the filtrate is limited to human beings and acquired after infancy. In addition, the filtrate itself is considerably more stable than a true toxin since its potency is relatively unaffected by heating and by age. These and other discrepancies between the action and properties of scarlatinal streptococcus filtrate and true toxins make it less certain that the former is a primarily toxic substance and suggest the possibility that the toxic effect of the filtrate in man might depend on an acquired allergic hypersensitivity.

According to the allergic hypothesis there exists an unsensitized state at birth but the streptococcus infections during early life and the absorption of specific antigenic substances produced by streptococci incite the production of specific antibody with a resulting cellular hypersensitivity. A later infection by the same organism, if accompanied by rapid antigen absorption, produces a generalized hypersensitivity reaction evidenced by the toxic syndrome of scarlet fever. This reaction desensitizes the patient by the removal of the specific antibody. Sensitized persons may, however, develop streptococcus infection characterized by slow antigen or allergen absorption, and under such circumstances the desensitization is accomplished gradually without production of a generalized scarlet fever reaction. The allergic hypothesis, however, assumes the possibility of another state with regard to the anti-scarlatinal antibody, that is, an anti-anaphylactic state characterized by the presence of a great excess of circulating antibody, which can combine with absorbed allergen in the circulation, and therefore prevent its reaching the sensitized cells. Clinical allergic reactions occur, apparently only when the antigen combines with antibody in the cells, and when antigen combines with free antibody in the circulation no clinical toxic reaction occurs. After an individual, as a result of excessive or continued absorption of the scarlatinal allergen, has developed a large amount of the antibody in the blood, he shows no clinical scarlatinal reaction to later streptococcus infection. It will be seen, therefore, that the allergic state of an individual with regard to the scarlatinal streptococcus allergen at any given time depends upon the amount and location of the specific antibody present. At birth he has none, and, therefore, there is no cellular skin sensitivity to the antigen (as shown by a negative Dick test), and there is no antibody demonstrable in the blood. When, as a result of later streptococcus infections the cells develop specific antibody in them, their sensitivity is shown by the development of a positive skin Dick test but still no circulating antibody is present. It is in this state of sensitivity that a streptococcus infection may be accompanied by the

scarlet fever syndrome, after which the skin cells are desensitized, the Dick test is negative, but there is still no circulating antibody. Indeed—and this is probably one of the most significant observations that favor the allergic theory—not only during the period of the rash, but after the rash and other toxic symptoms have disappeared, the erythrogenic antigen or toxin can be demonstrated in the patient's circulating blood, that is to say, the patient's blood serum produces positive Dick tests on susceptible or sensitive persons. Such an observation of antigen in the circulation after desensitization could be expected in the case of an allergen, but the presence of a true toxin in the blood after recovery from the specific toxemia would appear difficult to understand.

After desensitization, the absorbed antigen again stimulates the formation of specific antibody and sensitization returns, but when antibody is produced in excess by the cells, it appears in the circulation and the individual becomes anti-anaphylactic. In this state, he is immune to the allergic manifestations of antigen-antibody reaction, because when a subsequent streptococcus infection leads to further absorption of antigen, it is neutralized in the circulation and does not reach the sensitive cells. The amount of circulating antibody varies from time to time as recurring streptococcus infection increases its titer, or freedom from the infection leads to its gradual disappearance from the blood, and the consequent unmasking of the cellular sensitivity. The general reaction with rash and other toxic symptoms of scarlet fever occurs only in those persons who develop a hemolytic streptococcus infection with rapid antigen absorption when in this state of cellular sensitivity. During the early progress of the general reaction in scarlet fever, further combination of antigen with intracellular antibody can be suddenly halted by neutralizing the circulating antigen by the injection of an excess of free antibody thereby creating a state of transferred anti-anaphylaxis.

One final comment may be made on the two hypotheses. Whichever one comes ultimately to be accepted as the true explanation of the scarlet fever symptoms, each of them can be regarded as somewhat unique. If the streptococcus product is a true toxin, it is quite different from other such toxins, chiefly in its relatively weak toxic action and the fact that its activity seems limited to human beings. On the other hand, if the agent is an allergen, the presence of a specific neutralizing or inhibiting antibody and the hypothetical anti-anaphylactic state finds no analogy in other human allergic reactions.

The allergic hypothesis, however, is supported by a wealth of immunologic analogy, and has the merit of offering an adequate explanation for the various clinical phenomena observed in connection with hemolytic streptococcus infections, skin sensitivity tests, and scarlet fever.

THE PRODUCTION OF EXTRASYSTOLES BY MEANS OF THE CENTRAL NERVOUS SYSTEM

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THE occurrence of centrally inaugurated heterotopic impulses in the human heart was first reported by Lucke. Auricular extrasystoles were observed in a 54 year old man in association with a skull injury and severe *commotio cerebri*. A year after the injury the disturbance in rhythm had become even more marked, with the occurrence of fairly long series of successive extrasystoles. A second patient, aged 50, was observed, who for about seven years had suffered a compulsion polyuria resembling diabetes insipidus together with a slight fever which exhibited normal diurnal temperature variations. These findings required for their explanation the assumption of a lesion in the midbrain. The condition persisted for several years, after which cardiac symptoms developed, and ventricular extrasystoles were found in the electrocardiogram. No heart disease could be demonstrated. Lucke assumed a central production of the extrasystoles in both cases. In the first case, a *commotio cerebri* and in the second, a lesion in the midbrain had presumably led to a reaction in the region of the parasympathetic nucleus.

Lucke cited as the only previously known phenomenon of similar nature the case described by Kulbs of a 16 year old boy who developed a marked bradycardia following a severe emotional upset. The electrocardiogram showed a sinus bradycardia with flattening of the P-wave and ventricular automatism. This observation, however, is of no particular interest in connection with our present concern, the central origin of extrasystoles. Even though we do not believe that the sharp distinction made by Wenckebach and Winterberg between active and passive heterotopy is in complete accord with the multiple possibilities of origin of extrasystoles, still, the occurrence of a compensatory rhythm in a very slow sinus frequency presents a condition which can be termed a normal behavior of the heart, purely passive in origin. In this paper, however, we are considering the more or less "active" heterotopies in the sense of Lewis' "heterogenetic" contractions, that is, true extrasystoles. We are concerned less with the strict classification of extrasystoles or their sharp distinction from parasystoles, for example, than with as fundamental an understanding as possible of the conditions of origin of heterotopy in the individual case. It must be emphasized that responsibility for the origin of clinically observed extrasystoles can never be attributed solely to a single cause. The occurrence of an extra-

* Received for publication June 23, 1937

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systole is bound up with a definite situation originally created by the combined effect of many single conditions. From such a standpoint, and in view of the experimental results shortly to be described, it seems to us that in both cases reported by Lucke, the assumption of a central stimulatory effect as the initial cause of the extrasystoles is very likely valid.

If we assume the central origin of heterotopic stimulus formation in the heart, then the only pathway for the transmission of the stimulus that can be considered is that of the long cardiac nerves, particularly the vagus. Until recently the difficulty of such a conception lay perforce in the fact that no action of the vagus on the ventricles of the mammalian heart could be demonstrated. Direct vagus action is unlikely according to the most recent investigations as well. However, Scherf's very searching studies of the origin of extrasystoles show that there certainly exists an indirect vagus effect upon stimulus formation by tertiary centers. He was able to demonstrate a paradoxical effect on mammalian hearts poisoned with aconitin. Along with the normal blocking effect on the sinus node, there occurred ventricular extrasystoles. This indirect vagus effect is apparently to be explained by the arrival of the vagus affecting substance from the auricles to the ventricles, at the circulatory pathway, where it influences the damaged, peculiarly sensitive tertiary centers in paradoxical fashion. Engelhart found a much smaller content of vagus substances in the ventricles than in the auricles of the mammalian heart. Scherf found in this fact supporting evidence for his conception of the manner in which the vagus affects the formation of stimuli in the ventricle. To be sure, this still fails to explain why the vagus affecting substance, which has been brought to the ventricles by the circulatory pathway, does not have an inotropic effect as well (Rothberger and Scherf).

The reflex origin of extrasystoles has been recognized for a long time. Levy, in particular, was able to generate extrasystoles in this way in cats under chloroform narcosis by means of stimulation of the accelerans. Schott reported heterotopic stimulus formation in poisoned hearts as a result of clamping off the carotids. Schott has collected the extensive literature dealing with cardiac arrhythmias of reflex origin. Among clinical observations in this connection, only the findings of Lennox, Graves and Levine need be mentioned here. These authors found extrasystoles in 70 per cent of patients on a surgical service during operations on the head or neck, whereas during operations on other parts of the body extrasystoles were observed in only 40 per cent of the patients. They concluded from this that vagus stimulation was responsible for the increased occurrence of arrhythmias during operations on the neck.

Beyond the mere idea that the extracardiac nerves are effective in the development of extrasystoles, it has recently been possible actually to produce extrasystoles by central stimulation. Brow, Long and Beattie were able to produce extrasystoles by stimulation of the central vagus stump in cats.

which had been narcotized by means of chloroform, and they further succeeded in causing cessation of the extrasystoles by means of a properly directed incision in the hypothalamic region. This "extrasystole center" must of necessity have lain above the "Sherington level." Dikshit took up the experiments of Brow, Long and Beattie, and investigated the effect of substances injected into the ventricles of the brain on the production of extrasystoles. In this way heterotopic stimulus formation was inaugurated by means of the injection of acetylcholine into the lateral ventricle or into the third ventricle in the cat. Since both vagi were cut, transmission of the stimulus via the sympathetic was assumed. Caffeine and nicotine were found to have a quite similar effect. In several different experiments, no elevation of blood pressure, which may in itself cause extrasystoles, was observed. It was further possible to demonstrate the central origin of the extrasystoles, in that it was consistently possible to cause the extrasystoles to disappear very promptly by means of the intravenous or intraventricular injection of barbital. Dikshit further assumes that the stimulating substances exercise their effect on hypothalamic centers.

The effect of strophanthin when injected into the ventricles of the brain in dogs was investigated by Korth, Marx and Weinstein. The animals were trephined in a preliminary operation and it was possible to conduct the actual experiments without narcosis. This was important because in this way the observations could be carried out on the completely intact heart without previous sensitization. It was apparent that the strophanthin had exercised an extremely strong central stimulatory effect. The electrocardiographic tracings regularly showed a constant and very characteristic picture: a few minutes after the injection there developed first a sinus tachycardia, soon ventricular extrasystoles appeared, which quickly became preponderant and finally led to a true ventricular tachycardia with a rate of about 300 per minute. Thus, strophanthin, when given intraventricularly, causes a violent heterotopic formation of stimuli in tertiary centers. By means of intravenous administration of barbital, it was possible at once to cut short the ventricular tachycardia. Since the tachycardia could be maintained even after section of the vagus, it may be said that the transmission of stimuli is possible by way of both the sympathetic and the vagus. It is very difficult or indeed impossible, to distinguish between a vagal and a sympathetic effect (*Wirkweise*). (Scherf has pointed out the problems involved in the investigation of vagal and sympathetic effect on the origin of extrasystoles.) In addition to the above experiment, the effect of other highly active substances (histamine, acetylcholine, thyroxin, etc.) was investigated. It was found that the effect of strophanthin was distinctly different from that of the other substances tried. It may be mentioned here that, as a result of the experiments of Korth, Marx and Weinberg, there must be ascribed to strophanthin a specific effect in increasing cardiac activity by way of the central nervous system. The recognition of this fact would seem to be important for the understanding of the therapeutic effect of digitalis.

In consideration of all these facts, we are able to say that the possibility of the origin of ventricular extrasystoles on the basis of a stimulation of nerve centers in the brain has been experimentally demonstrated. The vegetative nervous system is primarily to be considered as the transmitting organ of the central stimulus.

We wish to report herewith a clinical observation on a patient with softening of the left cerebellar hemisphere, which furthers the hypothesis of a central nervous origin of ventricular extrasystoles.

CASE REPORT

A 58 year old coal dealer, J. G., came under our care March 8, 1937 with the following history. Three weeks previously he had suddenly been taken ill while doing gymnastic exercises. He felt a "tearing sensation" in the region of his heart. Immediately thereafter there were mild pressing sensations in the precordial region which, however disappeared after a few days. Nevertheless, shortness of breath developed on mild physical exertion, often accompanied by sweating and vomiting. Further, dyspnea, though less severe, also occurred during the night so that the patient had to sit up for a few minutes. Ten days before his entrance to the clinic his physician had diagnosed a mild cardiac weakness and advised treatment in the clinic.

The patient gave a history of severe diphtheria in childhood. He had had diphtheria again as a soldier at the age of 20, for which he was kept in the hospital for five weeks. Nothing was known of any other previous illnesses.

The examination showed enlargement of the heart, especially to the left, confirmed roentgenologically. On fluoroscopy the left auricle also appeared enlarged and small calcifications could be demonstrated in the mitral valve. The heart sounds were faint and no murmurs could be definitely heard. The pulse was absolutely irregular and the electrocardiogram showed auricular fibrillation. There was no edema, the liver was not swollen and percussion and auscultation of the lungs were negative. A diagnosis of mitral disease was made. Under strict dietary treatment the patient had a marked diuresis. He received verodigen from March 13 to March 20, corresponding to a total dosage of 2 grams of digitalis leaves. He felt distinctly better and was allowed to be up out of bed occasionally. The blood Wassermann reaction was negative. The systolic blood pressure varied between 110 and 125. On March 21, which was the fourteenth day of his illness, in the morning he suddenly complained of violent dizziness. He was found lying in bed, groaning and covered with a cold sweat. The patient was completely conscious and remained so. He said that after his bath he suddenly felt very sick, after which there was a sudden attack of severe vertigo so that he was able to reach his bed only with difficulty.

The examination showed the following findings. The color of the patient's face changed frequently and suddenly. marked redness with plainly perceptible warmth of the skin was followed by equally abrupt pallor. At short intervals beads of cold sweat appeared on his forehead and cheeks. The fingers of both hands occasionally showed a cyanotic bluish color and felt cold. He could not sit up in bed. A few minutes later it was observed that the left half of his face drooped. The folds of the face on the left side were smoothed out in comparison with the right. In addition, the patient complained of recurrent attacks of nausea. However, he did not vomit. The blood pressure remained unaltered. The tendon reflexes in his arms and legs were diminished, but equally strong on both sides, and pyramidal tract signs were not demonstrable. The pupils reacted normally to light and convergence. There was no nystagmus. There was no dysphagia.

Particularly striking was a noticeable irregularity of the pulse. While even the day before his pulse had been almost regular, even with the continuing auricular fibrillation, now suddenly numerous, or indeed showers of extrasystoles could be heard over the heart. The size of the heart was unchanged on percussion. The patient was given atropine 0.001 gm subcutaneously. About $\frac{1}{2}$ hour after the injection and an hour after the onset of the grave clinical picture the pulse again became more regular. The following day no extrasystoles could be noted. On the next day the patient failed noticeably. The marked vasomotor phenomena had ceased, to be sure, and only the vertigo persisted, and to a lesser degree than before. The patient died on the evening of March 22.

The autopsy revealed an embolus at the origin of the basilar artery and acute pale softening of the left cerebellar hemisphere. The mitral valve was markedly stenosed as the result of an old endocarditis, with scarring of the external papillary muscle. The left auricle was markedly dilated and hypertrophied. It could be assumed, accordingly, that the embolus in the cerebral artery had its origin in the left auricle.

In figure 1 we have placed together several different electrocardiographic tracings of this patient. The first tracing represents the electrocardiogram

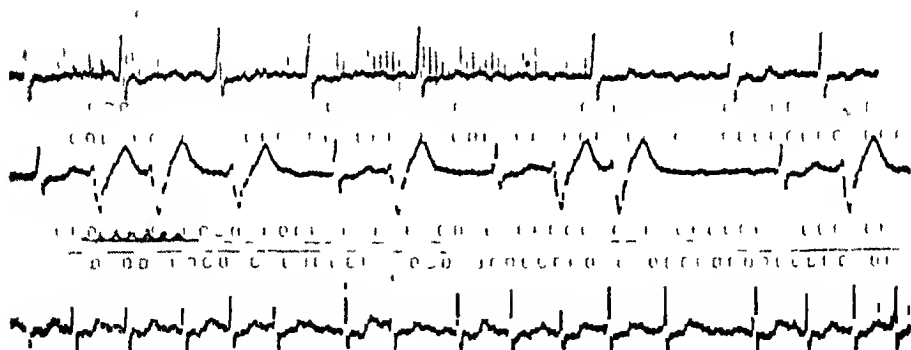


FIG 1

Top tracing March 19, before the attack
 Middle tracing March 21, $\frac{1}{2}$ hour after the attack
 Lower tracing March 22, the day after the attack

of March 19, the day before the apoplectic insult. Auricular fibrillation is apparent. The effect of the digitalis medication is seen in the reduction of the ventricular rate to about 60 per minute. The interval cannot be definitely determined because of the fibrillary arrhythmia. The second tracing is from the electrocardiogram of March 21, about one-half hour after the onset of the attack. Numerous ventricular extrasystoles, which occur in approximate alternation with normal beats, are apparent. In no instance do two normally conducted ventricular beats follow one another, giving the picture of bigeminy. The rate of the conducted beats shows no essential change from that of the preceding day. At least, no demonstrable tachycardia has developed. A rather long interval between an extrasystole and the next normally transmitted ventricular beat is evident. In the bottom

tracing we have finally the electrocardiogram of March 22. The extrasystoles have completely disappeared. The ventricular rate has meanwhile risen to approximately 140.

Thus in this case, in the course of an apoplectic insult affecting the left cerebellum, there suddenly developed showers of extrasystoles. The unusually marked vasomotor phenomena with simultaneous facial paralysis give rise to the presumption that medullary centers were sympathetically involved by the acute softening. We were unable to find any simpler and more obvious explanation of the extrasystoles than the supposition of a stimulating effect on the bulbar vagal center. In favor of this is also the fact that the extrasystoles were easily suppressible by means of atropine. We particularly wish to emphasize that the patient was fully conscious both during the insult and later, that the blood pressure remained unchanged and that there were no signs of circulatory failure.

It is further important to an understanding of these extrasystoles to note that the patient had received a total of 1.9 gm. of digitalis during the days preceding the onset of the insult. Just as in the case of the experimental extrasystoles produced reflexly by the cardiac nerves, previous intoxication of the heart was necessary, so in our case the digitalis treatment provided the necessary "sensitization" of the heart muscle. In the presence of an already existent readiness for heterotopic stimulus formation, the vagal stimulus resulting from the insult led to this manifestation of the heterotopy. Our observation presents a clear analogy to the paradoxical effect of a vagal stimulus on the formation of stimuli in the heart poisoned by aconitin as observed by Scherf. Even though the normal stimulus-inhibitory effect of the vagus on the sinus node is not demonstrable in our patient because of the auricular fibrillation, nevertheless we may assume a negative dromotropic effect of the vagal stimulus on the atrioventricular stimulus conduction. To be sure, it must be noted in this connection that the digitalization had already in any case led to a clearly evident retardation of ventricular activity, but during the insult the rate of conducted impulses is rather lowered than otherwise, or at any rate not increased. Quite in opposition to this is the extraordinarily increased stimulus formation in a tertiary center.

The foregoing observation may, I hope, serve to inspire greater attention to the occurrence of extrasystoles during cerebral affections. We may probably assume that such heterotopies are more frequent than might at first be suspected. Besides the considerable theoretical interest which the "central extrasystole" may claim, there is its practical significance. It may well be that, as Lucke has indicated, centrally produced disturbances in cardiac rhythm sympathetically involve the performances of the heart and that an affection of the heart of central origin is of essential prognostic significance in a primary cerebral disease.

SUMMARY

A brief review is given of our present knowledge of the possibility and the manner of origin of reflex and centrally originated extrasystoles. In this connection is presented the discussion of a clinical observation concerning the sudden occurrence of ventricular extrasystoles in a 58 year old man during an apoplectic insult with softening of the left half of the cerebellum. It is hypothesized that in this case the extrasystoles were originated centrally by means of a stimulatory effect on the medullary vagal nucleus. Finally attention is directed to the theoretical and practical significance of central extrasystoles.

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THE IMPORTANCE OF EMBOLISM AS A COMPLICATION OF CARDIAC INFARCTION *

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THE effect of sudden, non-fatal occlusion of one of the larger branches of a coronary artery is well known. The result, in brief, is the formation of an ischemic infarct involving that portion of the heart muscle supplied by the obstructed vessel, the so-called *myomalacia cordis*. The extent of this process depends on various factors, the more important being the size of the occluded vessel and the extent of development of vascular channels capable of taking part in the formation of a collateral circulation. The variability of the process is of practical importance at the bedside because certain clinical features are directly dependent on the presence of certain pathological changes. If the necrosis of the affected area of heart muscle does not involve the pericardium, localized pericarditis, a valuable clinical sign, does not develop. If the necrosis does not involve the endocardium lining the infarcted area, mural thrombi do not develop and secondary embolism, at least from this source, does not occur. It is well known that the necrotic process much more frequently involves the endocardial than the pericardial surface of the infarcted area. Wolff and White¹ state that mural thrombi almost always develop over the infarct. The valuable study of Meakins and Eakin² shows, however, that this statement is probably too sweeping, as mural thrombi occurred in only 46.7 per cent of their 62 autopsies. It is important to realize that, on account of the frequency with which the left descending branch is involved, both ventricles are frequently the site of mural thrombi, although Meakins and Eakin's figures indicate that they are about twice as common on the left as on the right side. It is clear, however, that in many patients who have suffered an occlusion there is an opportunity for the detachment of emboli from both ventricles and for their lodgment both in the pulmonary and the systemic circulations.

There is no doubt that some of the earlier writers on coronary occlusion failed to realize the importance of embolism as a complication of the resulting infarction. Other observers noted its occurrence and commented on it. Thayer³ in his article of 1923 clearly recognized the importance of the condition and diagnosed it during life. Gordiner,⁴ in his report on a series of 13 cases published in 1924, suggests that the sudden arterial plugging of the vessels of the brain, viscera or extremities indicates involvement of a branch of the left coronary, while signs of pulmonary infarct suggest involvement of the right coronary or its branches. Hamman⁵ in 1927, ap-

* Received for publication June 16, 1937

pears to have been the first to specially emphasize the significance of embolic phenomena, particularly in diagnosis, and since his article numerous authors, including Allan,⁶ Harrington and Wright⁷ and Parkinson and Bedford⁸ have stressed their importance

As might be expected, there is a decided difference between the figures covering the frequency of embolism based on postmortem examinations and those covering emboli diagnosed by clinical observation

TABLE I
Site of Emboli as Shown by Autopsy

Author	No of Autopsies	Lung	Brain	Kidney	Spleen	Limb Vessels	Aorta	Mesenteric Artery
Meakins and Eakin	62	47	4	14	9	11	2	
Parkinson and Bedford	83	7	1	9	8	2	1	3
Wolff and White	19		2	6	2			1
Total	164	54	7	29	19	13	3	4

Table 1, covering 164 autopsies, shows that 130 emboli were discovered in the organs of the 164 subjects. This does not mean, however, that 130 out of 164 *patients* had emboli, because multiple emboli in the same patient are by no means rare. Table 2, covering 945 patients observed clinically,

TABLE II
Number of Patients with Clinically Detectable Emboli

Author	No of Patients	No of Patients Showing Emboli
Anderson ⁹	9	1
Blumer	175	27
Conner and Holt ¹⁰	287	42
Gordinier	13	3
Howard ¹¹	165	17
Hyman and Parsonnet	51	17
Levine	145	17
Parkinson and Bedford	100	8
Total	945	132 = 13.9%

shows that 132 or 13.9 per cent had embolic manifestations recognizable during life. Inasmuch as many small emboli fail to give rise to recognizable clinical phenomena and even fairly large emboli may be clinically latent, it seems certain that many more than 13.9 per cent of patients with coronary occlusion have embolism. However, it cannot be assumed that the clinical phenomena resulting from arterial occlusion in the brain, viscera or extremities are all of embolic origin. Some of them are doubtless due, as Meakins and Eakin point out, to thrombosis occurring coincident with or

subsequent to the coronary thrombosis. Owing to the difficulty of deciding, even on the autopsy table, whether a given lesion is thrombotic or embolic, exact figures as to the relative frequency of the two lesions are impossible to obtain, and, as a matter of fact, the decision is of academic rather than clinical interest.

A knowledge of the organs most frequently the *site* of embolism is of practical importance. Table 1, based on autopsy material, shows that the lungs are most frequently involved, followed by the kidneys, the spleen, the peripheral vessels, the brain, the mesenteric vessels and the aorta. Table 3,

TABLE III
Site of Emboli as Observed Clinically

Author	No of Emboli	Lung	Brain	Kidney	Spleen	Ex- tremity	Periph- ery	Aorta
Blumer	35	16	9	1		6	3	
Gordinier	4	2	1	1				
Howard	17	9	3	2		2	1	
Levine	17	5	7	1	1		2	1
Parkinson and Bedford	8	3	3	1	1			
Total	81	35	23	6	2	8	6	1

based on 81 collected clinical cases, shows that clinically also the lungs are most frequently involved, followed by the central nervous system, the vessels of the extremities, the kidney and surface vessels, the spleen and the aorta. It is obvious that pulmonary and cerebral emboli would be those most likely to be clinically recognized because they so frequently lead to obvious symptoms and detectable clinical signs. The same is true of occlusion of the arteries of the extremities, which usually causes readily recognizable and characteristic changes. Small emboli in the spleen and kidney could be much more readily overlooked, especially in patients so seriously ill as many of these patients are.

The *period* in the disease at which emboli are likely to occur varies within wide limits. In a collection of 40 patients with emboli observed by the author or taken from Levine's series¹² just 60 per cent showed evidences of embolism within 10 days of the occlusion. The remaining 40 per cent showed embolic phenomena between the eleventh and the thirty-eighth day. In some instances embolism occurred almost simultaneously with the coronary lesion, but this took place in only two out of 40 patients and it is possible that the lesions were thrombotic rather than embolic. Embolism on the second day is not uncommon, one such case seen by the writer occurred when the patient was unfortunately upset while being carried upstairs in a chair. The largest number of embolic phenomena occurred from the seventh to the tenth day. The number of cases with definite information as to the time of embolism is, obviously, much too small for accurate statistical purposes and these figures must be regarded as merely suggestive.

The *clinical manifestations* of embolism in these patients were the usual ones. In the pulmonary cases sudden pain in the chest, hemoptysis, cyanosis, shock and physical signs of local pulmonary change were usually present. In the cerebral cases the picture varied with the localization of the lesion, partial or complete hemiplegia, with or without aphasia, being the most common lesion in the severer cases. In some patients minor effects such as ptosis of one eyelid, visual hallucinations, strabismus or temporary amblyopia were observed. The involvement of peripheral vessels, almost always in the lower extremities constituted a serious problem when it occurred. Gangrene commonly resulted and frequently the condition of the patient was so poor that active surgical intervention could not be seriously considered and, on account of very low blood pressure, the use of vasodilators was hazardous. Involvement of the skin vessels was seen occasionally, resulting in superficial areas of gangrene. Sudden attacks of local peripheral pain without obvious signs, were present in one of my patients.

There is a small group of cases which require special consideration, i.e. those in whom embolic phenomena occurred months or even years after the coronary occlusion.* One patient, personally observed, had a cerebral accident, presumably an embolism a year after the occlusion. In one of Levine's patients a left hemiplegia developed eight months after the occlusion. Hyman and Paisonnet¹³ cite two patients who died of cerebral embolism one three years and one five years after a coronary occlusion. One can hardly assume, I think, that the emboli in these patients originated in a mural thrombus which developed over the infarcted area at the time of the attack, for the fact that these patients recovered from the attack made it probable that these thrombi became organized and harmless as a source of emboli. It is possible but not probable in view of the usual postmortem findings in healed infarction, that thrombosis is more likely to develop at the site of a former infarction than elsewhere, even years after the original lesion. It is more likely perhaps, that the emboli in these patients had their origin in intracardiac thrombi developing elsewhere in the heart as a result of poor circulation, just as they not infrequently develop in apparently well compensated cases of mitral stenosis. The question cannot be conclusively decided without more postmortem evidence.

The most important bearing which the question of embolism following cardiac infarction has is its influence on *prognosis*. It is certainly true that many of these patients recover from pulmonary infarcts but, as McNee¹⁴ has shown, the detachment of pulmonary emboli large enough to cause death may occur. Furthermore, there can be little question that the added strain associated with the development of one or more pulmonary infarcts may prove too severe a burden on the damaged heart. In my limited experience the development of cerebral embolism during the acute phase of cardiac

* These cases are not included in table 3

infarction has usually resulted disastrously. Recovery after late cerebral emboli may undoubtedly occur. Embolism of the larger vessels of the limbs has a most serious effect on the prognosis, for the impaired circulation and the low blood pressure encourage the development of gangrene and the outcome is commonly a fatal one.

So far as *treatment* is concerned, it would seem that the frequency with which mural thrombi are present in coronary occlusion serves to emphasize the necessity for prolonged and absolute rest during the acute phases of the process. It also justifies the attitude of many clinicians regarding the avoidance of medication with digitalis, unless there is some very definite indication for its use, such as auricular fibrillation.

The following conclusions seem justifiable.

1. In patients with cardiac infarction due to coronary occlusion mural thrombi are present over the endocardial surface of the infarcted area in about 50 per cent.

2. These mural thrombi may be limited to one cavity, but are frequently present in both the right and the left side of the heart.

3. Fragments of such thrombi are detached and produce clinically recognizable embolic phenomena in about 14 per cent of patients with cardiac infarction.

4. Embolism is most likely to occur during the first 10 days following a coronary occlusion.

5. Embolism of branches of the pulmonary artery is the most frequent type, but is less serious prognostically than cerebral embolism and embolism of the larger vessels of the extremities.

6. The frequency of such emboli emphasizes the importance of absolute and protracted rest and the avoidance of medication by digitalis, unless especially indicated, in the treatment of cardiac infarction.

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KAPOK AND MOLDS AN IMPORTANT COMBINATION

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IN a former study of kapok ("silk floss") we¹ showed that a considerable number of patients with asthma have been relieved of their symptoms simply by eliminating kapok from the environment. We pointed out that the fibers of new kapok, freshly removed from the pod, have a high luster and resiliency, that extracts of them rarely give skin tests, that this kapok fresh and new, does little harm. Old kapok, however, which has been used as the stuffing of pillows, mattresses, and furniture, for some time, has a dull appearance. The fibers are dry and brittle, and readily break down into a fine dust. Extracts of old kapok give positive skin tests in many patients and the dust of old kapok is a frequent cause of asthma and other allergic disorders. The new and the old material have physical and chemical properties which are quite different and the content of the skin active principle appears to run parallel with the other properties.

What causes these changes due apparently to "age" in kapok? Van Leeuwen² believed that fungi were the causative agents. He observed that *Aspergillus fumigatus* which had been isolated from old kapok and which in itself gave negative reacting extracts, was able to convert non-reactive kapok into reactive kapok if it was allowed to grow on the non-active material. On the other hand, G. T. Brown³ in his recent studies on the importance of molds to allergy was unable to demonstrate any changes occurring in sterilized kapok after its inoculation with cultures of molds and other microorganisms including various species of *alternaria*, *aspergilli*, and *mucor*.

The observations of Cohen⁴ and his fellow workers with raw cotton suggest that other factors can be responsible. They found that non-reactive cotton which had been sterilized and kept sealed for several months became reactive. The changes had taken place in the absence of viable microorganisms, and moreover, as the materials were in sealed containers, it is doubtful whether other external factors such as oxygen or carbon dioxide could have been important in bringing about the changes observed. The evidence presented was more in favor of internal factors that were thermostable and which perhaps possessed properties similar to those found in enzymes.

These previous observations have not explained the clinical findings.

* Received for publication May 14, 1937.

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There is need for additional studies, and in this present work, we have endeavored to investigate a few of the factors which we believed were important in the case of kapok.

EXPERIMENTAL

At the outset it was necessary to ascertain what effect sterilization by heat might have on the skin active principles of the various materials that would be used in the work. Suitable quantities of old kapok, old cotton linters, and of house dust, were sterilized for three hours at a pressure of 15 pounds per square inch. After cooling, each substance was extracted with Coca's solution and each extract was tested in the skin of seven patients. The skin tests with the extracts of the sterilized materials gave results which were in every case identical with the results of skin tests with extracts of the original unsterilized materials. Thus, whatever the skin active principle in old kapok, in old cotton linters, and in house dust may be, it is not affected by ordinary sterilization.

A second experiment was designed to study the effect of time alone on sterilized material. Cohen's experiment was repeated. Samples of kapok fiber obtained from the fresh opened pod were placed in large vials which were then sealed with rubber caps and sterilized for three hours in the autoclave. To equalize the inside and outside pressure of the vial during sterilization, a hypodermic needle plunged through the cap was used as a vent. At the end of sterilization, the needle was removed and the vials further sealed with melted paraffin. At this stage, the fibers as seen through the glass of the vial appeared to have lost some of their luster and to have darkened in color. The vials of sterilized new kapok were then placed as follows. One was set upon the window ledge so as to be exposed to the sunlight. Another was placed in a covered box that was put in a laboratory drawer. As a control for any possible changes occurring due to temperature, a third vial was placed in the rear of the laboratory ice box. All vials were left undisturbed for a period of six months. At the end of this time, the materials within the vials were removed, weighed, and extracted with Coca's solution on an equal weight volume basis. They were sterilized by Seitz filtration. All the extracts appeared alike and no visible difference could be noted between them and other extracts of freshly isolated pod kapok. Skin tests with the three extracts were made in 18 subjects who were known to give good skin reactions to old kapok but the results were entirely negative. Moreover, these same tests were repeated in 14 of the 18 subjects and again gave the same negative results. We thereby concluded that, at least within a period of six months, no significant changes had occurred in sterilized and sealed pod kapok whether it was exposed to sunlight, protected from light, or kept at temperatures of 8°, or at ordinary room temperature.

In a third experiment, the effect of dryness was investigated. A mode-

rate quantity of sterilized pod kapok was placed in desiccators over calcium chloride and over concentrated sulphuric acid. These likewise remained undisturbed for six months after which time the kapok was removed and extracted at once and taken to the clinic for testing purposes. In a series of 10 old kapok sensitive individuals, all extracts of the dried kapok gave negative results in all instances. Apparently prolonged exposure to a dry atmosphere does not cause any appreciable change in the skin reactivity of new kapok. If loss of moisture is the cause of breakdown in the kapok fiber, it alone is not the cause of the development of skin reacting factors.

At this point in the study, the supply of pod kapok gave out. (We were informed that the Dutch Government has prohibited the shipment of kapok pods and seeds from its colonial possessions.) We were forced to be content with the use of new kapok from a freshly opened bale*. This material, while not as inactive as the pod material so far as skin tests were concerned, was distinctly less reactive than old kapok.

In a fourth experiment, we sought to rule out the possible effect of oxygenation and carbon dioxide action. We reasoned that if either of these processes was important to the changes, an increased concentration might speed up the reactions so that their effects could be observed within a comparatively short time. To study this matter, three large Florence flasks were half filled with bale kapok and sterilized for three hours in the autoclave. After this treatment, we observed as before that gross changes similar to those mentioned in the case of pod kapok were present. The fibers had less luster and were of a darker shade of yellow. The flasks were allowed to cool over night and the next morning they were fitted with sterilized stoppers and tubing so that the atmosphere within the flasks could be easily changed. Into one of the flasks, cotton filtered oxygen was allowed to pass for a period of 15 minutes. The oxygen supply was then shut off and the feeding and exit tubes clamped tightly. In similar fashion, the atmosphere in the second flask was changed to carbon dioxide. The third flask was left sealed and served as a control. Thereafter, over a period of three months and at intervals of every three days, the oxygen and carbon dioxide in the first two flasks were renewed by the same technique. Meanwhile the flasks were kept at room temperature. At the end of three months, the material in each of the three flasks showed no changes in the gross appearances. It was removed and extracted. The three extracts were adjusted to an equal weight volume basis and were tested in 14 sensitive subjects. In all cases, it was impossible to distinguish any difference in the skin tests between the extracts of the material which had been exposed to either oxygen or carbon dioxide and that of the control. The evidence would indicate that the presence of concentrated oxygen or carbon dioxide alone over a prolonged period of time was not an important factor in activating relatively inert new kapok.

* The material was obtained through the courtesy of the Kapo Products Company.

In a supplementary experiment and with the purpose of additional control, oxygen and carbon dioxide respectively, were bubbled at rapid rates through extracts of old and new kapok for periods of two to eight hours. Skin tests with extracts treated in this manner gave results that were comparable in all respects with the untreated extracts. Apparently the skin active principle in kapok extracts is not easily, if at all, affected by continuous contact with pure oxygen or with pure carbon dioxide.

Meanwhile, other investigations of the possible effects of microorganisms were in progress. Extracts of the pure cultures of the common molds isolated from old kapok and described in a previous paper by Conant and the writers⁵ were tested on a group of 54 old-kapok-sensitive individuals. Ten patients gave moderately positive reactions with the extract of chaetomium species, nine with the extract of *Aspergillus niger*, nine with the extract of penicillium species, and seven with the extract of *Rhizopus nigricans*. These results are comparable to those of Brown³ and of Feinberg⁶ both of whom have tested large groups of allergic patients with extracts of the more common molds.

So far then, it has been demonstrated, first that extracts of new, unused, and freshly obtained kapok give negative skin tests, that this new material may be held in the laboratory under various conditions for considerable periods of time and still its extracts will give negative tests. Second, that extracts of the cultures of molds readily isolated from old used kapok gave positive skin tests in only a few of the old-kapok-sensitive patients.

Evidently, the many positive skin tests obtained with old kapok extracts depended neither upon the substance itself—the kapok fiber, nor upon the molds themselves that might grow in it. Perhaps, however, they depended upon the combination of molds plus kapok, that certain molds growing on this particular substrate would cause chemical changes which would result in the development of skin reactive principles.

To test this idea, the following series of experiments were carried out.

From Professor Weston we learned that certain molds have a predilection for certain substrates, that even in a single species, different individuals may have habits of growth which are quite different, one from another, and therefore, that it is important in any inoculation experiment, to use those strains which there is reason to think might grow well on the particular substrate. The idea of obtaining the inoculum by washing the old used material and using all the organisms obtained in the sediment was developed.

The procedure employed was as follows. Generous samples of the various old materials—old kapok, old cotton linters, and house dust—were wet down well with sterile salt solution (0.9 per cent) and the mixtures were allowed to stand and extract for approximately one hour. Then, the materials were stirred vigorously. The mass was squeezed in gauze and the dirty fluid was collected in a sterile container. The sediments were separated by centrifuging at high speed, adding increments of 40 c.c. of the fluid until a

sufficient amount of sediment had been secured. The supernatant fluids which contained extracts of old kapok, of old cotton linters, or of house dust, were discarded, but when later the sediments were washed in three changes of salt solution, the washings were saved and pooled for control purposes. The washed sediments were suspended in sterile distilled water and transferred to sterile atomizers from which they were sprayed in liberal quantities into flasks containing the substrate. These flasks were prepared in this way. Liberal quantities of kapok fiber from the bale, cotton fibers from new unopened bolls,* and finally, the fibers of commercial non-absorbent cotton, were finely cut with scissors, placed in florence flasks, sterilized in the autoclave, and finally spray inoculated. After inoculation with the spray, the mouths of the flasks were covered with inverted beakers and placed in large tin cans that were fitted with tight covers. To secure a high degree of humidity, the lower portions of each can were packed with moistened sphagnum moss. The relative humidity within the cans was checked at frequent intervals through two small holes in the covers and was always found to be above 80 per cent. In this experiment, all flasks were prepared in duplicate, and to eliminate the possibility of cross contamination, separate cans were used for each inoculum and its set of substrates. The cans were kept in the laboratory at ordinary room temperature. At the end of 60 days, one flask of each duplicate set was removed from the cans, the other flask being taken out after 120 days. Grossly, most of the flasks showed evidence of the growth of molds among the fibers—a few colonies black, yellow, green, or gray were seen here and there and more of them in the 120 day flasks, but the growth was not uniform or constant for any one sediment-inoculum or any one substrate. The heaviest growth seemed to be in the flask containing boll cotton which had been inoculated with old cotton-linter sediment, thus supporting the suggestion of Dr. Weston that certain molds have a predilection for certain substrates. Non-absorbent cotton seemed unable to support a growth of molds, for none of the flasks containing this material showed any gross change even after standing in the moist chamber for 120 days—and this was regardless of which particular inoculum was used. At the end of 60 days, the material in the first set of flasks was extracted by adding Coca's buffered phosphate solution to it and allowing the mixture to stand over night. The extracts were adjusted on a uniform weight-volume basis and were filtered first through paper and then through a Seitz wafer. At the end of 120 days, the second flask of each set was removed, examined, and extracted in the same manner.

Skin tests with the extracts were made as soon as they were prepared. Controls were provided as follows. Similar flasks of the vegetable fiber substrates were inoculated with mixtures of known mold cultures while others were inoculated with a bacterium—*B. subtilis* being chosen. Another set of flasks was placed in the moist chambers without any inoculation.

* The cotton bolls were obtained through the courtesy of The Murray Company, Dallas, Texas.

The sediment inocula were tested separately to see whether they alone might give skin tests. The washings of these sediments were pooled and saved as described, but skin tests with them were always negative. Each of the sediment suspensions was planted on duplicate dextrose agar slants, one set being incubated for 48 hours and the other for one week. At the end of these incubation periods, the whole cultures were extracted with Coca's buffered saline and the extracts passed through sterile Seitz filters. Skin tests with each extract gave negative reactions in a group of kapok-house dust-cotton linter-sensitive subjects.

TABLE I

Skin tests with extracts of bale kapok, boll cotton, and non absorbent cotton which had been sterilized first and then inoculated with dust sediments and microorganisms. Test subjects all skin sensitive to old kapok.

Sub- ject	60 day Extracts																	
	Inoculum																	
	Kapok Sed			Linter Sed			Dust Sed			Mold Mixt			<i>B. Subtilis</i>			Controls		
	BK	BC	NC	BK	BC	NC	BK	BC	NC	BK	BC	NC	BK	BC	NC	BK	BC	NC
1	0	0	±	±	+	0	±	±	0	0	0	±	0	0	0	0	0	0
2	0	±	0	±	+	±	±	±	0	0	0	0	0	0	0	0	0	0
3	0	±	0	±	+	±	±	±	0	±	±	0	0	0	0	0	0	0
4	±	±	0	±	+	±	0	±	0	±	0	0	0	0	0	0	0	0
5	±	±	0	0	0	0	0	0	0	±	±	0	0	0	0	0	0	0
6	0	±	0	0	+	0	0	0	0	0	0	0	+	0	0	0	0	0

Sub- ject	120 day Extracts																	
	Inoculum																	
	Kapok Sed			Linter Sed			Dust Sed			Mold Mixt			<i>B. Subtilis</i>			Controls		
	BK	BC	NC	BK	BC	NC	BK	BC	NC	BK	BC	NC	BK	BC	NC	BK	BC	NC
1	+	0	0	0	+	0	0	0	0	+	+	0	0	0	0	0	0	0
2	±	+	0	+	0	0	0	+	+	0	0	+	0	0	0	+	0	0
3	+	+	0	+	+	0	+	+	0	0	0	0	±	+	0	0	0	0
4	0	0	0	+	+	0	0	+	0	+	0	+	+	+	0	0	0	0
5	+	+	0	+	+	±	+	+	0	0	+	0	+	+	+	0	0	0
6	0	0	+	0	0	0	+	0	0	+	0	0	0	0	+	0	+	0
7	+	+	0	+	+	0	+	+	0	+	0	0	+	0	0	0	0	0

BK = Bale kapok BC = Boll cotton NC = Non absorbent cotton

The results of skin tests with the extracts of the inoculated flasks are shown in table 1

These results were not striking with any of the 60 day extracts and for the most part the reactions, where positive, were distinctly less than those given by the extracts of the corresponding old material. The greater frequency of positive reactions with the 120 day extracts is good evidence that the development of the active skin-test principle is associated with the amount of growth. The boll-cotton, cotton-linter sediment combination which showed the greatest amount of mold growth yielded extracts which gave the greatest number of positive reactions of any of the combinations. The negative reactions with the extracts of the controls indicate that the time element alone is not an important factor in the formation of the active principle.

The results do not show any relationship between the three inocula. Boll cotton inoculated with each of three sediments gives different results in each instance. This observation is interesting as the studies of Cohen et al. indicated that the active principles of house dust and old cotton linters had a common source. The negative skin tests with non-absorbent cotton however inoculated also indicates that the principle necessary for the growth of molds is similar to that necessary for the production of skin tests—the principle being removed in the manufacture of non-absorbent cotton.

Sterilized materials yielded only a meager growth after a period of 60 days. This raised the question whether sterilization in itself had affected the materials so that they became less suitable for the growth of molds. To investigate this possibility, the 60 day set of the previous experiment was repeated, using unsterilized materials. Inoculation with the common mold mixture and with the *B. subtilis* culture was omitted in this experiment, the controls being simply the unsterilized, uninoculated material which had been incubated in the same way. When this unsterilized material was inoculated with the mold containing sediments, a marked growth was obtained. Not only were there isolated colonies here and there between the fibers, but the contents of the flasks containing boll cotton and bale kapok all showed a dirty gray color with numerous black and yellow colonies. In contrast, the non-absorbent cotton flasks had no obvious growth and the uninoculated flasks showed no obvious growth.

The results of skin tests with extracts of the flask contents after incubation for 60 days in the moist chamber are shown in table 2. The results here are quite different from those obtained with the sterilized material. As the table shows, skin tests were not only positive but were often well marked. Bale kapok and boll cotton gave positive results in almost all instances and regardless of whether they were inoculated with the sediments obtained from old kapok, from old linters, or from house dust. If left uninoculated, however, the results were negative. This last is surprising because one would suppose that the crude material might contain in itself

molds of various sorts which would develop and produce changes similar to those in the inoculated material. Perhaps the time (60 days) was too short for full development or perhaps the samples obtained even though unsterilized were yet more or less free of the common molds. The former possibility is more likely. It is noted in this experiment also that non-absorbent cotton was not changed by mold growth sufficiently to produce a skin-test active extract.

TABLE II

Skin tests with extracts of bale kapok, boll cotton, and non-absorbent cotton not sterilized but inoculated with various materials. 60 day extracts. Test subjects all skin sensitive to old kapok.

Subject	Inoculum											
	Kapok Sed			Linter Sed			Dust Sed			Controls		
	B K	B C	N C	B K	B C	N C	B K	B C	N C	B K	B C	N C
1	+	+	0	+	++	0	0	+	0	0	0	0
2	++	+	0	++	++	0	++	++	0	0	0	0
3	++	+	0	+ 2	++	2 0	+	+	0	0	0	0
4	0	0	0	+	+	0	0	0	0	0	0	0
5	+	+	0	++	0	0	+	+	0	0	0	0
6	+	+	0	++	++	0	+	+	0	0	+	0
7	0	0	0	+	++	+	0	±	+	±	0	0
8	++	++	0	++	++	0	++	++	0	0	+	0
9	±	+	0	+	++	0	0	+	0	0	0	0

B K = Bale kapok B C = Boll cotton N C = Non-absorbent cotton

These experiments demonstrate that the cause of the breakdown in the kapok fiber as well as the development of the skin test active principles in extracts of old kapok is the growth of molds upon the vegetable substrate. Skin tests with the molds alone are usually negative, skin tests with the kapok itself are negative, but when molds and kapok are combined, positive skin tests became easily demonstrable. The observations explain the clinical experiences previously described and point again to the great clinical importance, that is to say, the danger in the use of old kapok in the home. The same considerations apply to cotton linters. These vegetable fibers support the growth of molds and so develop skin test active principles. Non-absorbent cotton has, in the process of manufacture, lost something which is important for the support of mold growth as well as for the production of skin reactive extracts. Presumably, the same argument will

apply to all untreated fibers of vegetable origin in contrast to those of animal origin—like hair and feathers

SUMMARY

1 Steam sterilization of vegetable fibers (cotton and kapok) changes the material in some way so that molds will not grow well upon it

2 Time alone produces no change in kapok fiber which has been sterilized, regardless of whether this time be passed in the light, the dark, or the cold

3 Drying has no effect in producing the skin-test active principle

4 Oxygen and carbon dioxide have no effect even though the fibers are kept in the atmosphere of these gases for as long as three months

5 Molds, however, will cause changes in both boll cotton and bale kapok, especially if the molds are taken from samples of old kapok, old cotton linters and house dust. However, extracts of the inoculum itself give no skin tests

6 The skin-test active principle is directly proportional to mold growth so that

7 It is more marked in the 120 day cultures than in the 60 day cultures, and

8 It is much more marked when unsterilized material is inoculated

9 The experiments demonstrate that the active skin-test principle in commercial kapok depends upon the growth of molds in the kapok (vegetable) fibers

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THE CLASS METHOD IN THE TREATMENT OF ESSENTIAL HYPERTENSION

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WE are able to treat successfully such diseases as syphilis, allergic asthma or congestive heart failure because we have a good deal of accurate knowledge concerning their etiology and pathology, in the case of other conditions such as scurvy, malaria or pernicious anemia the lack of such knowledge did not prevent the discovery of a specific cure. Essential hypertension belongs to a third group of clinical entities, the etiology and pathology of which remain to a considerable extent obscure and for which there is no specific treatment. Fortunately perhaps, our profession has never permitted a deficiency in its knowledge of the exact nature of a disease to stand in the way of its therapeutics, so that there is no lack of suggestions for the care of the patient with hypertension. Ayman¹ collected within a decade over 200 accounts of procedures directed toward the relief of this condition. The remarkable fact is that they were all successful! He analyzed 35 of these articles in some detail, and found that practically every one reported complete or partial symptomatic relief, and in the majority a moderate to marked reduction in blood pressure was reported.

The "good results" obtained are not comparable to the cure of scurvy by the administration of orange juice or the relief of the symptoms of pernicious anemia by liver therapy. They consist in a subjective sense of improvement, the relief of a variety of symptoms, and a fall in the blood pressure level. All these results can be duplicated in patients treated only by suggestion, as Ayman has demonstrated. It does not follow that they are illusory. Such knowledge as we have of the etiology and pathology of hypertension is consistent with the clinically observed improvement which follows a variety of therapeutic measures if we consider that the two factors common to them all are sedation and the prevention or relief of vasoconstriction. Suggestion, by inspiring a sense of confidence as to the benefits of treatment, relieves worry, quiets the patient and permits him to relax. There is no good theoretical reason why suggestion should not thus accomplish sedation and vaso-relaxation as effectively (in kind and perhaps occasionally in degree as well) as luminal, alcohol, the nitrites, watermelon seed extract, mistletoe or surgery of the sympathetic nervous system.

I do not wish to seem to advocate suggestion as a method of stopping the pathological process which results in an arterio-capillary fibrosis or a

* Received for publication April 7, 1937

necrotizing arteriolar sclerosis, beyond the point suggested by many literal minded persons that "nervous tension" may possibly play some part in furthering the progress of such lesions. Confining ourselves to the consideration of the mere psychic benefit to the patient, it is pertinent to recall that the symptoms presented by patients with high blood pressure in its early stages are identically those complained of by psychoneurotic patients. Some observers have even concluded that "the early symptoms associated with essential hypertension are of psychic origin" ²

If we may conclude that sedation and relaxation are the two objectives to be sought in the treatment of our hypertensive patients, we are in a position to cease following the will o' the wisp of specific cure and to settle down to the development of a well planned therapeutic regime. Only thus can we rescue the hypertensive patient from the neglect that he now receives. Our interest in him must not be casual and intermittent, as it now is for the most part, but continuous and purposeful.

A method of demonstrated value in the treatment of the psychoneuroses might be expected to be helpful in relieving the symptoms of hypertension. The success of the "Thought Control" class established by Dr. Joseph H. Pratt ³ at the Boston Dispensary in redeeming a very considerable number of these patients suggested to us that a similar method applied to the treatment of patients with hypertension might be equally valuable.

Certainly the power of suggestion is "stepped up" when the suggestion is administered to a group. When a patient joins a group his individuality merges with it, and his individual resistance to suggestion is overcome by the contagion of the group response to its leader.

Again, the class method is helpful to the members of the group because of the morale which is developed in any association of persons working toward a common end. It is always difficult for the patient to carry out any regime of treatment "on his own." The difficulty is comparable to that of self-instruction in painting or drawing or gymnastics or Latin or mathematics. Class instruction encourages competitive striving for results, it causes the members to try to emulate those who are most successful, it develops a spirit of cooperation and enthusiasm which is possible only in a group with a common objective.

We have for several months conducted a "Hypertension Class" recruited from patients attending the medical clinic at the Boston Dispensary. The only requirement for membership is a high blood pressure. The attendance of patients with advanced renal failure is not encouraged, but neither is it denied them.

Our purpose is to present to these invalids a program of living which will enable them to consistently live at the optimum level of well being which is possible for them. This is in many or perhaps the majority of instances surprisingly high.

The program is built about a threefold approach which can be illustrated

graphically by a triangle each side of which represents one aspect of the treatment. This constitutes the Rule of the class (figure 1) and is demonstrated at each meeting.

By "Medical Care" we mean all treatment available in the clinic apart from participation in the class. This may be medical or surgical and in-

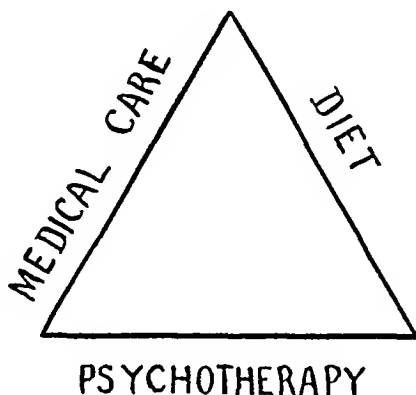


FIG 1 The Rule of the Class

cludes such matters as the treatment of varicose veins, or diabetes, sinusitis or congestive heart failure. We make no attempt to supervise or direct this adjuvant treatment, but prefer to permit the patient to attend to the care of his own needs as these are discovered by his regular medical attendant. We simply urge upon him the necessity for his giving ordinary sensible attention to his general health.

The second arm of the triangle, "Diet," is a rather arbitrary affair. To the average patient, a Diet is like Voltaire's God: if It did not exist, he should have to create It. I believe it is more desirable to build upon this hope than to antagonize our patients by denying the importance of a proper dietary. The diet chosen is advised first on the grounds that it may be essentially beneficial. It certainly is not harmful. People who by necessity followed this diet in the Scandinavian countries during the war years are reported to have shown a decreased mortality not only from hypertension but also from other diseases, especially those accompanied by degenerative processes in the cardiovascular system. This diet is that which Hindhede⁴ has promulgated for many years. It consists simply of potatoes, baked and eaten with the skins intact, dark bread and butter, milk, and apples or other fresh fruit. The members of the class are permitted to vary this rather Spartan, but on the whole well balanced and certainly economical fare by occasional mild lapses on holidays or when they go out to dinner and do not wish to be thought eccentric. If the diet is adhered to as well as most patients do adhere to it, we need not worry much about calories.

The base of the triangle is in fact the basis of our whole systematic method—the use of suggestion and psychotherapy. In the class this takes

the form first of education and explanation. The relatively benign course of essential hypertension is stressed, a plausible theory of its pathological physiology consistent with the knowledge we have is presented, and the importance of physical and nervous strain in the development of symptoms is emphasized. Abundant material is available here for many lectures, which are received with interest and appreciation, and more, with a feeling of reassurance and often the alleviation of fear.

Further, the psychic origin of the symptoms of early hypertension is explained. Without attempting any individual psychoanalysis, we simply point out over and over again the important rôle of the emotions, of apprehension and worry and unpleasant thoughts in the genesis of symptoms. The field here is too great to discuss within a paragraph. The fact is that all middle aged hypertensives (and many others) need a spiritual director, or call him a psychiatrist, or a personality worker if this seems preferable, and if as physicians we fail to utilize our opportunities in this direction we are not doing justice to our patients.

Finally, at each class meeting, the importance is stressed and the practice insisted upon, of regular and systematic relaxation. We should like to advocate that the "progressive relaxation" of Jacobson⁵ be developed and practiced by all of our patients, but the method is too time consuming and instruction in its use requires too much individual attention for it to be practicable. It is possible to obtain results with a less elaborate technic. We have a five minute relaxation period at each meeting during which all persons in the room are asked to individually follow the demonstration by the leader. Here again, it is difficult to convey briefly the really profound effect which can be attained by the proper conduct of this five minute period of complete silence and repose. The class members practice their "relaxation exercise" once, twice or three times daily, if they are able, during the week.

A feature which is important, and never omitted, is the giving of "testimony" by the older members. The success of those who have been practicing the tenets of the class is a powerful factor in starting the new members off in the proper spirit of optimism and earnest attention to the rules. Those who have benefited by their attendance are ever willing to stand up and say so to the other members of the group, and their testimony is more effective than any amount of lecturing or grave advice.

Our results over a period of several months have justified our expectations. Patients of course report the relief of such symptoms as dizziness, pain in the neck, hot burning sensations in the head, insomnia, and "shortness of breath." The uniformity with which they report that they "feel fine" (when formerly they presented a variety of symptoms) in itself testifies to a new mental attitude if not to any modification of the underlying pathological process. Some of our patients have shown no striking change in the level of their blood pressures, but in two-thirds of those who have

made three or more visits to the class a fall in pressure of from 18 to 46 millimeters of mercury has been observed

Our aim is not, however, primarily to reduce blood pressure, it is rather to aid these patients to attain an optimal level of well being. The approach is frankly largely psychologic. We feel that we have accomplished a worth while result if our patients lose their fears, adapt themselves to their condition and become optimists rather than pessimists, and we view our method as an application of well known and well tried principles rather than as a new form of treatment. In the clinic it enables us to utilize these principles far more effectively than they can be used in the individual interview.

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PAROXYSMAL VENTRICULAR TACHYCARDIA REPORT OF THREE CASES, MECHOLYL USED AND INEFFECTIVE IN TWO

By NEUTON S. STERN, M.D., F.A.C.P., *Memphis, Tennessee*

THE comparative rarity of paroxysmal ventricular tachycardia, and the opportunity to report upon the ineffective use of mecholyl in proved cases suggested the presentation of these cases

CASE REPORTS

Case 1 S. B. C., female, single, aged 75, seen in consultation with Dr. Otis S. Warr. She was admitted to the Baptist Memorial Hospital December 25, 1936, for pain in her chest, cough and expectoration. Diagnosis was made of bronchopneumonia and hypertension, the blood pressure being 155 systolic and 110 diastolic on admission. Three days later she became semicomatose, cyanotic, with shallow breathing of the Cheyne-Stokes type. Blood pressure 135 systolic and 85 diastolic. An

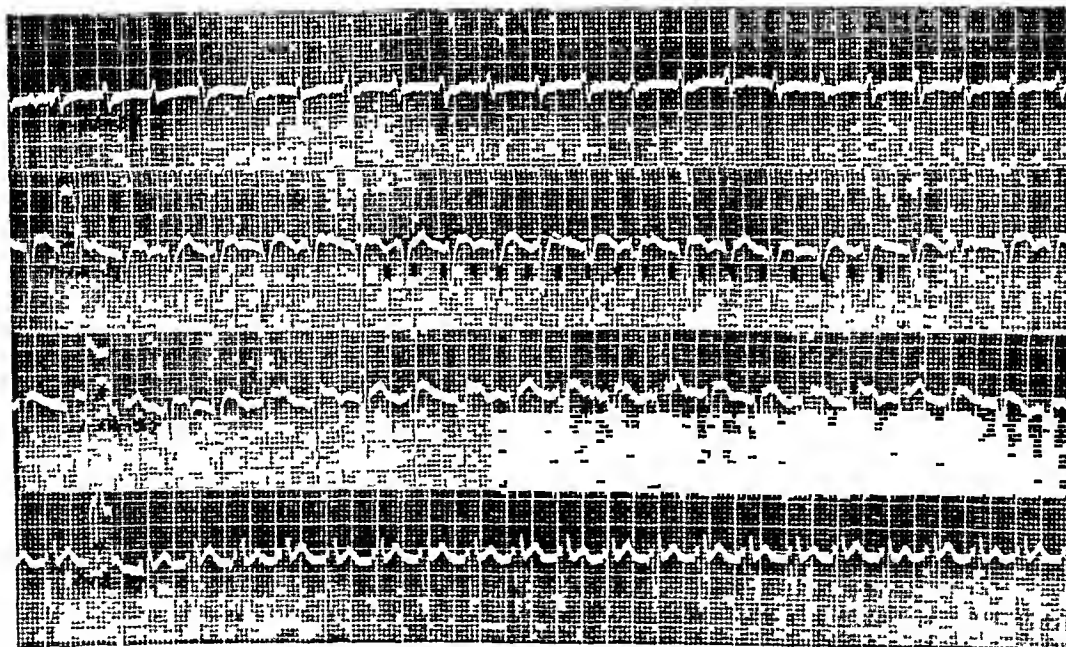


FIG 1

oxygen tent was used with relief, and consciousness returned. On the following days the pressure varied from 104 systolic and 80 diastolic to 160 systolic and 108 diastolic, and once to 180 systolic and 90 diastolic. Breathing continued to be somewhat difficult. The findings by roentgen-ray suggested unresolved pneumonia with

* Received for publication June 18, 1937

clear areas possibly due to abscesses. The heart rate was rapid but regular, 100 to 120. Roentgen-ray therapy to the chest was tried January 5 and 8, 1937. On January 9, dyspnea increased, and the heart showed a gallop rhythm. The blood pressure tended to stay about 160 for the next few days. Dyspnea, tachypnea and râles in the chest indicated left ventricular failure, and the sudden attack of December 28 with drop of pressure suggested coronary occlusion.

On January 12, an electrocardiogram (figure 1) was made at the bedside. The ventricular rate was rapid, 167, the rhythm was regular, but the complexes showed slight variations in the length and shape of the principal deflections, and considerable

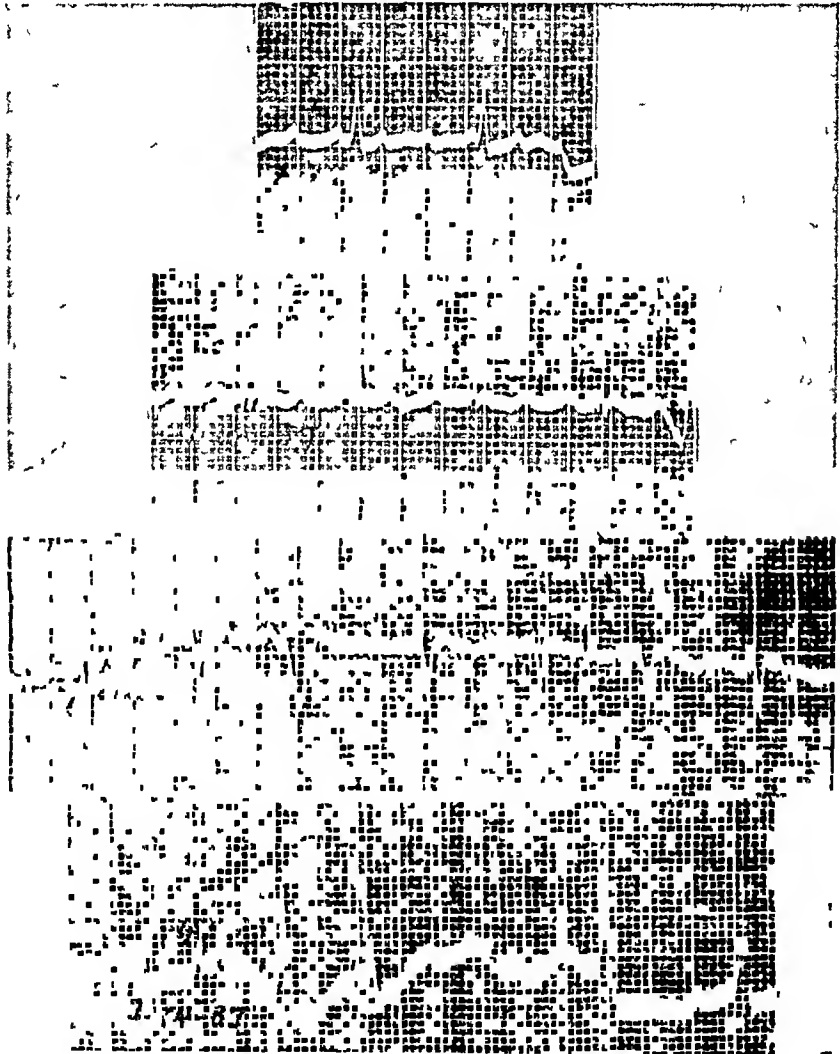


FIG 2

variations in the curve between these deflections. These variations were believed due to small P-waves superimposed on the ventricular complexes, falling at different times in the cycles, and were sometimes visible and sometimes buried. On this interpretation the auricular waves seemed to be regular and of a rate of 273. The interpretation of these electrocardiographic findings was Auricular flutter, complete A-V dissociation, ventricular tachycardia (probably nodal).

A similar curve was obtained on January 13

On January 14, the ventricular rate was very much slower (115) and the complexes had changed in shape (figure 2) The auricular rate was 286 The diagnosis was made of auricular flutter, with complete heart block In the light of this evidence it was believed that the rapid ventricular beat of the previous day had been due to paroxysmal ventricular tachycardia, the focus of origin being ectopic, below rather than in the node

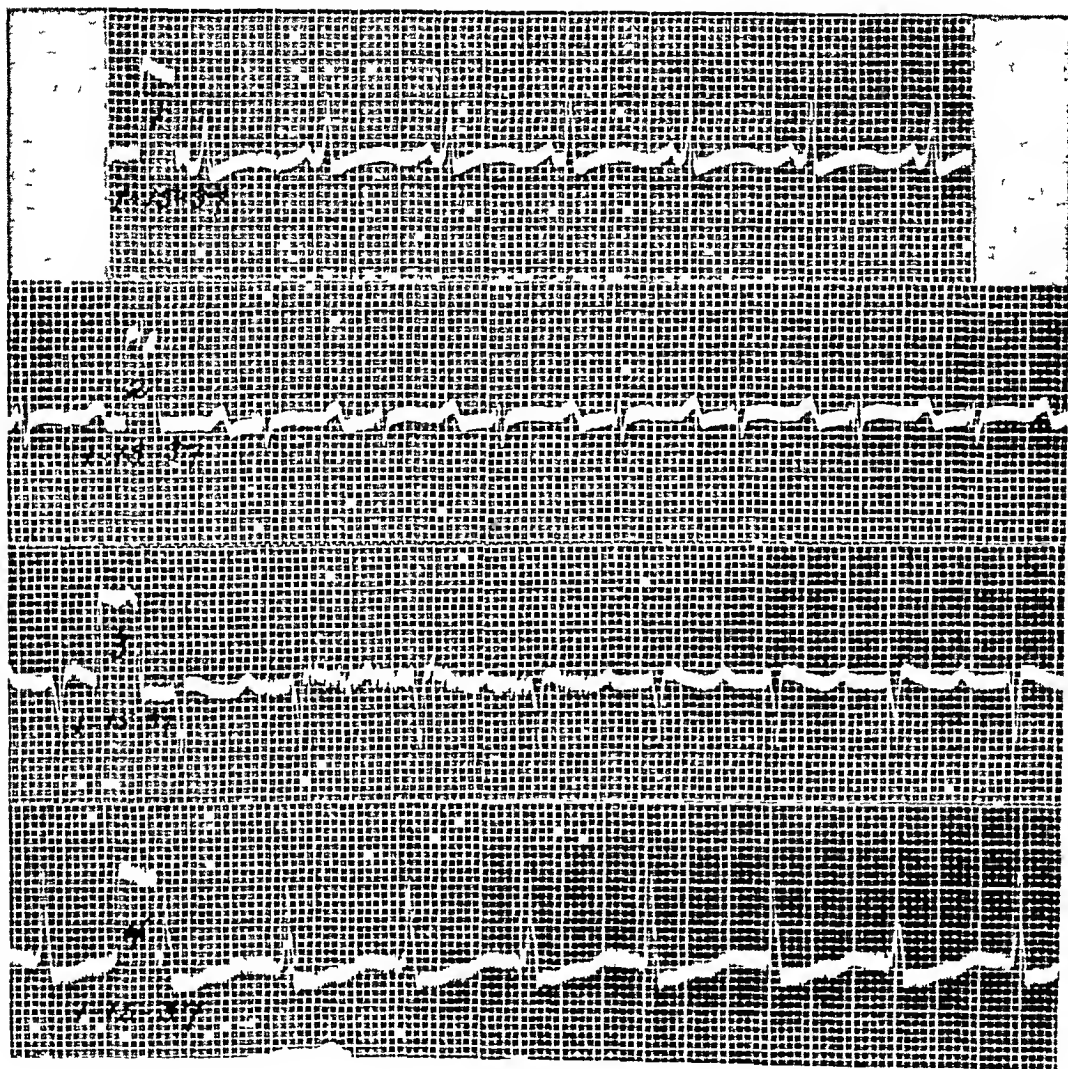


FIG 3

On January 15, the electrocardiogram (figure 3) showed a ventricular rate of 105 Left axis deviation was present, T_1 was slightly upright, T_{2-4} were not definitely discernible In Lead I, the P-wave was quite close (about 0.08-0.09 sec) to the ventricular complex, and the relationship was 1:1 This P was not inverted, and hence not retrograde In Leads II and III the P-R interval was markedly prolonged, being about 0.24 sec in Lead II, and about 0.26 sec in Lead III Possibly no block was present during the taking of Lead I, but more likely the conduction was so

delayed that each P induced not the ventricular beat immediately following but the next one. It was also possible that complete block still existed with auricular and ventricular rates very nearly the same, but the relationship altered between taking the leads as it might be made to by a ventricular premature beat.

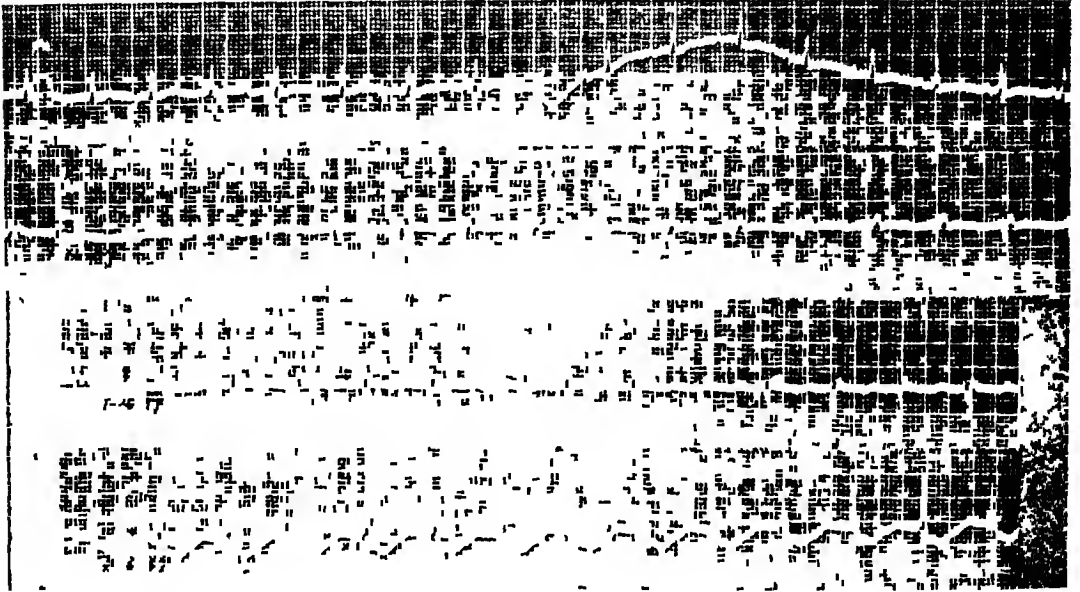


FIG 4

On January 16 the electrocardiogram (figure 4) showed complete heart block. The ventricular and auricular rates were so nearly the same that it required many beats before the relative positions of P and QRS were definitely altered. This was probably the status on the fifteenth.

January 17 Heart rate 90

January 21 Died Autopsy not secured

Among the diagnoses were Paroxysmal ventricular tachycardia, paroxysmal auricular flutter, complete heart block, coronary sclerosis and occlusion.

Case 2 A P, male, aged 8, was seen in consultation with Dr W R Graves, December 19 1936. He had been seen on December 14 by Dr Graves. At that time he complained of abdominal pain and rapid heart beat. He was uncertain which came first. The pain disappeared in a few hours. His past history was negative except for scarlet fever one year ago.

Tachycardia was found, the heart rate varying in rate from 160 to 180 with slight irregularity present. An electrocardiogram taken at the Baptist Memorial Hospital revealed a tachycardia of ventricular origin. On December 19, the rate was still rapid, the apex beat was about 3 cm beyond the midclavicular line. A soft systolic murmur was present. The liver was slightly enlarged. No edema was present. After a test dose of quinidine sulphate of gr iii (0.2 gm) he was given four doses of 4 grains each at two hour intervals. The apex rate dropped to about 120. My electrocardiogram (figure 5) was taken at this point. Mecholyl (0.010 gm) subcutaneously caused vomiting, but was without result on the tachycardia. A few days later the paroxysm ceased spontaneously.

On January 15, 1937, the heart was only slightly rapid. There was a short squirty systolic murmur at the apex which was at the anterior axillary line. No râles were present, and no edema. Under the fluoroscope, the heart was seen to be

very large, with rounded borders, the left being close to the lateral border of the thorax. The electrocardiogram on this day showed left axis deviation.

About March 17, a paroxysm of tachycardia started accompanied by vomiting. Vomiting and the rapid pulse continued in spite of mechloryl, quinidine and glucose, and on March 19 he died. Autopsy was not secured.

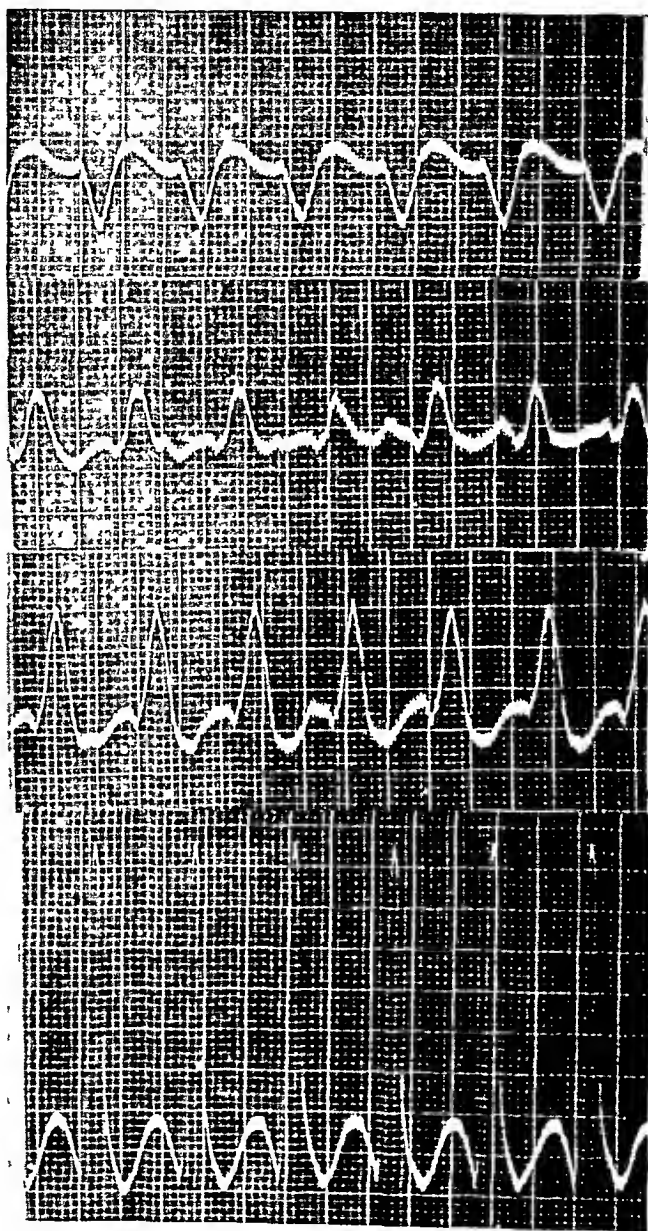


FIG 5

Case 3 O. H., Jr., was first seen in 1932 at the age of seven. Two months before he had had influenza, followed by some exhaustion. Three weeks before he suffered an attack of tachycardia (rate over 200, rhythm regular) which lasted for two and a half days. He was given quinidine sulphate, and the attack stopped in a

few minutes (coincidence?) Two weeks later he had another attack which lasted 48 hours. It was not affected by quinidine. The rhythm was regular during the attack but irregular at the offset. The attacks seemed to be associated with mild digestive upsets, nausea and constipation. He had a skin eruption on the flexor surfaces of his forearms which came and went, and which the dermatologist, Dr E. R. Hall, thought to be allergic.

When seen by me there was no circulatory disturbance, and his physical examination was entirely normal. Fluoroscopy showed no abnormality. Electrocardiography (January 4, 1932) gave an entirely normal tracing except high T_1 (4.5 mm) and T_2 (5.0 mm).

He was seen again November 9, 1933. He had had three attacks of paroxysmal tachycardia in the previous three or four weeks, each lasting some length of time. Physical examination showed a heart rate of 112, a questionable systolic murmur at the apex which seemed to be just beyond the nipple.

On November 29, 1935, he was seen again. In the interval he had been examined by Dr. Hugh McCulloch in St. Louis, who it was reported thought the heart was slightly enlarged. On physical examination I found the apex to be 7 cm to the left of the midline in fifth intercostal space, palpable just beyond the nipple. The right border was 1.5 cm to the right. There was marked respiratory sinus arrhythmia. The sounds were normal. The rate was 72, the blood pressure 100 systolic and 60 diastolic.

The six-foot teleroentgenogram showed these measurements: RM 37 cm, LM 66 cm, T 103 cm, internal thoracic 19.5 cm, L 110 cm.

The electrocardiogram showed sinus arrhythmia, S_1 deeper (5 mm instead of 2.5 mm), and altered T-waves. T_1 was upright (5 mm), T_2 upright (5 mm) with slightly elevated RT_1 and T_2 takeoff, T_3 inverted (1 mm), T_4 upright, and variable (from 2 to 4 mm). R_2 upstroke slightly slurred. Lead IV was taken from the left chest, fourth and fifth interspaces at left border of the sternum to the left leg.

During the following year, an attack was stopped in six minutes by meclocholyl 0.010 gm.

On November 18, 1936, he had an attack of tachycardia which lasted through the next day. Prior to this, he had had a cold with slight fever. During the year he had taken quinidine sulphate prophylactically, but recently had not taken any for several days. With the attack he had pain in the heart area like a hammer, "worse than an earache." He had had pain five times with attacks. The pain was not radiating. On November 21, another attack of tachycardia occurred, and pain began at once, subsiding later, leaving a bruised feeling.

On examination, the apex rate was counted as 176, and was sufficiently irregular to give the impression of auricular fibrillation. The blood pressure was 80 systolic and 60 diastolic. The first sound at the apex had a soft squirting quality.

An electrocardiogram was taken (figure 6) which showed a tachycardia of ventricular origin.

Meclocholyl 0.010 gm was given without result. The attack ceased the next morning.

On January 29, 1937, another attack appeared following a slight sore throat with fever (100° F) the previous day. Quinidine sulphate gr. i had been taken the previous evening and the morning of the attack. The attack ceased spontaneously just before he was seen, but an electrocardiogram was taken which showed a high T_1 (5.5 mm) with RT_1 takeoff about 1 mm high, a high T_2 (9 mm), cone shaped, with high RT_2 takeoff (1.5 mm), a high T_3 (3 mm) with RT_3 takeoff slightly high (0.5 mm), a diphasic T_4 (plus 4.5 mm, minus 1.5 mm).

On June 9, 1937, he was in good health. Pulse 76 and blood pressure 105 systolic and 60 diastolic. The pulse showed slight sinus arrhythmia. The sounds were nor-

mal The heart shadow on fluoroscopy suggested slightly the sabot shape The teleroentgenogram measured RM 35 cm , LM 67 cm , T 102 cm , L 133 cm , internal thoracic 234 The electrocardiogram showed T₁ upright (5 mm) with RT₁

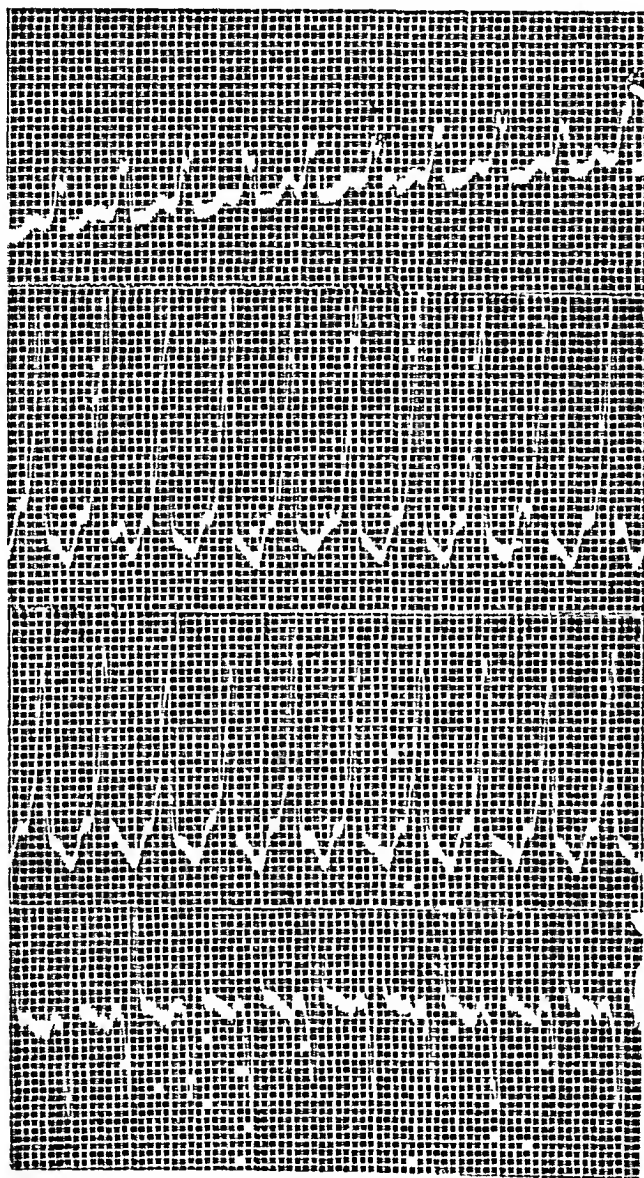


FIG 6

takeoff only slightly elevated, a high T₂ (3.5-4 mm) with high RT. takeoff (1 mm) , T₃ was inverted (0.5 mm) with RT. takeoff practically isoelectric, T₄ variable and diphasic (plus 1-2 mm , minus 1 mm)

The changes in this electrocardiogram, the abnormal T-waves and RT takeoffs, suggest that there is definite myocardial disease present in this boy

SUMMARY

1 Three cases are presented each showing a paroxysm of ventricular tachycardia. Each heart yielded evidence of organic heart disease, though such evidence is electrocardiographic only in Case 3.

2 Mecholyl was used in Cases 2 and 3, but was unsuccessful in terminating attacks that were proved to be of ventricular origin.

3 One case presented the paroxysm of ventricular tachycardia during an attack of paroxysmal auricular flutter, and later showed a complete heart block during the flutter, and with normal auricular rhythm.

AN ARTICLE CONTRIBUTED TO AN ANNIVERSARY VOLUME IN HONOR
OF DOCTOR JOSEPH HERSEY PRATT

OTTMAR ROSENBACH, PIONEER IN THE DEVELOPMENT OF THE CONCEPT OF FUNCTIONAL DISEASE AND FUNCTIONAL DIAGNOSIS IN INTERNAL MEDICINE¹

By HYMAN MORRISON, M D , *Boston, Massachusetts*

OTTMAR ROSENBACH holds a place among the notables in medicine by virtue of the part he played in the development of the concept of functional disease and functional diagnosis. This idea of recognizing and treating disease before structural pathology had actually taken place marks an epoch-making advance in internal medicine, historically in line with its several evolutionary stages.

First, there was the descriptive period dominated by Sydenham (1624-1689). A keen, painstaking observer, Sydenham re-introduced the old Hippocratic method of studying disease at the bedside and during epidemics, and grouped symptoms into clear-cut disease pictures previously undifferentiated or unrecognized.

The next stage began with Morgagni (1682-1771), founder of pathology, and reached its height during the first half of the 19th century in the clinico-pathological schools in France and England with the towering figure of Laennec. New methods of physical examination were invented, notably percussion and auscultation, many diseases were newly described, but more important was the correlation of clinical observation with pathological lesions demonstrated post-mortem.

In the middle of the same century a third step forward was made when physiological and chemical methods became an integral part of clinical investigation. Magendie in France defined medicine as "nothing but the physiology of the sick man" and similarly Virchow in Germany taught that "disease is nothing but life under altered conditions." It became insufficient to men like Traube merely to describe disease, nor would the lesions found in organs after death explain all the symptoms before death. Only by combining experimentation with observation and pathology could internal medicine attain the status of an exact science.

Then came the bacteriological era with Pasteur and Roux and Koch and Ehrlich and Behring. A new technic was developed, and stress was laid on etiology and specific therapy.

All along many new clinical entities were studied and classified. As they became more familiar, they came to be recognized not only in their typical or classical form, but also in their atypical guise, the *formes frustes*. Furthermore this trend led medical thought to concern itself with disease

¹ Received for publication March 17, 1937.

in its incipency, when alterations were only functional and not yet structural. In 1867 Kussmaul began to employ the stomach pump in gastric dilatation with stasis. In 1871 Leube studied gastric function with a test meal and demonstrated occasional deficiency of acid in the stomach. Others described gastric hypersecretion—permanent and transitory, and absence of hydrochloric acid in cases of gastric cancer. In the field of heart disease the term “cardiac insufficiency” was introduced about the same time by Von Dusch. These initial investigations were continued by Rosenbach, a



O. Rosenbach.

disciple of Leube, and it was he who first elaborated the concept of functional disease.

THE MAN—BIOGRAPHICAL DATA

Ottmar Rosenbach (b 1851, d 1907) was a native of Silesia, of Jewish parentage, the son of a physician, the nephew of Ludwig Traube and also related to Weigert, Ehrlich and Albert Fraenkel. After completing his medical studies at Breslau and Berlin (interrupted for a time by service in the Franco-Prussian War) he became assistant in the medical clinic at Jena in 1873 under Leube and Nothnagel where he remained for four years.

Among other studies, his experimental and clinical researches on the motor function of the digestive and circulatory apparatus, already initiated by his chief, were instrumental in inaugurating a new movement in internal medicine. He continued and elaborated this work in Breslau where he went in 1877, there he came under the influence of Julius Cohnheim. In 1887 he became medical director in the Allerheiligen Hospital, and in the following year extraordinary professor in the University. By this time he had attained eminence both as investigator and clinician, but in 1893 he resigned from the hospital and in 1896 from the University because of differences of opinion. He then moved to Berlin, where he remained to the end of his life, in 1907, devoting himself entirely, except for some consultation practice, to the writing up of previously completed scientific problems—"like an explorer, reaching home, putting in order, and classifying leisurely, the rich treasures he had collected during his travels."

HIS WORK AND MOTIF

In 1909, two years after his death, a selected collection of his writings, in two volumes, was published by Walter Guttman, friend and former pupil, including a biographical essay and a list of all his works. Even a brief perusal of this list will readily disclose that Rosenbach was a man of unusual energy and versatility, a fearless thinker whose interest reached out over the entire realm of medicine and beyond into the sciences, natural history, and philosophy. In all, 258 publications are enumerated, 14 in book form and the rest monographs and contributions to various periodicals and encyclopedias. Besides, there are mentioned many unpublished manuscripts on various topics—physics, chemistry, psychology, languages, and social medicine. This is the more impressive, when we are told that writing was a great task for him, that he would rewrite each work a number of times before it was published, that many manuscripts remained unpublished because they did not satisfy him, that he would even recall a work already in print for the same reason, that he kept on working to the very end in spite of several years of silent suffering from a malignant abdominal tumor and heart disease, and that all this was done in a relatively short span of life (1851–1907) aside from research, teaching, and hospital and consultation practice. But to work as long as one's strength would allow was the plan of his life, and even on his death bed it was his greatest concern that just those works which he considered most important—one on illusions and the other on certain physical and cosmic problems—were not completed.

I don't write merely for the sake of writing, or to create sensation, or out of desire to fight. I write for the love of science the tools of which are careful observation, extensive experience, logic and sober critique, and the object of which is the recognition and emancipation of the spirit from the yoke of tradition, and not the subjugation of mankind under the shackles of infallible authority. I write for love of the medical profession, whose true representative in my opinion is not the laboratory man, the theoretician or the specialist, but the physician in the fullest

sense of the word, who standing in the midst of life shows fullest sympathy for the patient (armed with the weapons of science but not tied slavishly to authority) I write from the point of view of the physician who recognizes that the suffering of man is an expression of unfavorable energy relationship or psychic influences which can be prevented or cured through no one point of view or method and only seldom through specific curative measures

I write, finally, out of the deeply rooted conviction that the laity also must not follow authority slavishly, but must be drawn only through study and example to better insight into all health problems. Insight will only then be complete when modern men will have learned again to sympathize with the patient to the highest degree instead of looking upon him as a source of contagion, shut out of human society in blind fear

This quotation is from the introduction to his book "The Problem of Syphilis", hence the last allusion. He detested the prevailing hysterical fear of contagion in syphilis, tuberculosis and other infectious diseases, leading to an almost total disregard of the importance of natural predisposition and resistance to infection

That he should speak in this manner was clearly justified by the wealth of his experience both in the laboratory and in the clinic and by the value of his concepts. Merely citing some representative topics from the list of his publications will give an estimate of the scope of his activity. By far the largest number of his contributions concern themselves with diagnosis, every phase of it to date was covered—physical, clinico-pathologic and pharmacologic, bacteriologic, neurologic and functional. He constantly emphasized, however, that "diagnosis must not be an end in itself or a means for systematic classification—it is the triumph of the art of medicine only when it furnishes a direct basis for prophylaxis and therapy"

In physical diagnosis there are papers on various aspects of auscultation and percussion and paracentesis, on the diagnosis of pleural exudate and on the effect of large pleural effusion on the circulation, on foreign bodies in the bronchi, on Cheyne-Stokes breathing, on cyanosis, on edema, on the diagnostic significance of reflexes, on pulsation of the liver and of the abdominal aorta, on carcinoma of the stomach, on Heberden's nodes, on intermittent hydrarthrosis of the knees, on the coincidence of tabes dorsalis and aortic insufficiency, on fever and antipyretics and thermometry, on chlorosis and other anemias, on diabetes and on the uric acid diathesis, on syphilis, on seasickness, and on epileptic and uremic convulsions. In 1893 there appeared his classic on "Diseases of the Heart and Their Treatment," and in 1903 a translation of his splendid monograph on "Diseases of the Pleura" in the American edition of Nothnagel's System of Medicine

Another group of papers is on clinico-pathologic and pharmacologic topics: studies on pigment formation in gastrointestinal and metabolic disturbances, on the significance of indicanuria, on tests for bile and glucose, on paroxysmal hemoglobinuria, and on albuminuria, on the antagonism between iodine and the salicylates, on sulphonal and amylhydrate, on the use and misuse of sodium bicarbonate, on chloral hydrate as a sedative in certain

types of dyspepsia, on the effect of digitalis on tissue and visceral tonus and on morphia

To neurology he contributed experimental studies in neuritis and on the physiology of the vagus, papers on hemiplegia, on paralysis of the recurrent laryngeal nerve, on the behavior of reflexes in sleep, on the mechanism of sleep, on cardiac neurosis, and on psychotherapy. Particularly noteworthy in this field was his work on the recurrent laryngeal nerves done in his earlier years at Breslau, when interestingly enough his first teaching experience was in the otolaryngological department because that happened at the time to be the only available position. It is noteworthy, also, because his intuitive power is here displayed to a high degree. On the basis of a single case carefully studied and on the critical analysis of similar cases reported in the literature he evolved in 1880 the now well known law "that in compression of the recurrent laryngeal nerve, first the dilators of the glottis suffer and only later are the constrictors involved sympathetically." With further clinical experience he amplified it to the effect that "frequently in affections of the nerve trunks or the central organs the flexors become paralyzed much later than the extensors." This work was recognized seriously only after Felix Semon confirmed it by independent investigation of a large number of cases.

HIS ATTITUDE TO BACTERIOLOGY AND TO EXPERIMENTATION IN MEDICINE

Although an aggressive opponent to the domination of medicine by the bacteriologic laboratory he recognized fully the biologic importance of bacteriology. "The value of bacteriology as a science cannot be over-emphasized," he said, "and it is capable of mestimable development." His very first publication in 1875 (after his inaugural dissertation in 1873 on a case of calculous pyelitis with perforation into the ascending colon) was on a new kind of grass green sputum, the color of which he demonstrated by cultural methods to be due to spores. Other papers were on malaria and cholera, and his controversy with Robert Koch on tuberculin involved a number of publications on tuberculosis and the tubercle bacillus. In a very stimulating book, "Aizt contra Bacteriologie," available in English translation, he sums up his attitude toward bacteriology and toward experimentation in medicine and also his general philosophy of medicine.

It took no small measure of courage to stand up practically single-handed against Koch, the latter then at the pinnacle of his career, to combat tuberculin as a therapeutic measure, or to disprove the statistics employed in claiming the efficacy of diphtheria antitoxin. But, though a most kind and generous man in personal relationship, he would never compromise in what he considered the truth. "No one will probably refuse to acknowledge that, uninfluenced by the fascinating opinion of the day, I have endeavored to discuss difficult problems from actual experience and in as many different lights as possible, with incisive criticism but objectively withal. The future will

decide whether I am right or wrong, and in what respect I have gone too far. Children who are now at play will in the end be our judges." Time did prove him correct in his controversy with Koch.

Just because he had experimented much, he warned against over-estimation of experimental conclusions, especially the drawing of conclusions concerning man from results on animals. "Injection diseases and infection diseases," he insisted "are two entirely different phenomena" and he early expressed his conviction that one must consider the clinic and observation at the bedside as predominant in the realm of human pathology. What reason can there be to assume identity of processes, when one taking place clinically shows in every case the effect of individuality and predisposition, whereas the case called forth by experiment does not at all manifest these factors? In disease caused by injection (experiment) there is scarcely any consideration of defensive and compensatory measures, whereas in human infection these factors appearing gradually produce a series of functional and structural changes. Only in a few infectious diseases, such as anthrax, acute military tuberculosis, and tetanus, is there an approach to identity between the disease process in man and in experimental animals. Even in these instances, in the case of the disease in man there are the phases of invasion, incubation, and gradual systemic involvement whereas in the experimental animal the organism is suddenly overwhelmed avoiding all defensive agencies, so that invasion and the height of the disease are almost synchronous. If it is considered, further, that comparatively enormous quantities of microbes are utilized for the injections, the differences between disease as observed clinically and disease called forth by experiment will be better appreciated.

I am fully aware that my criticism will be called a retrogression, but I am convinced that it is well-founded. I do not demand that exclusively one domain and one method of investigation should be cultivated, but I merely give it as my opinion that the clinic and the observation at the bedside should be considered the only scales by which results obtained through other methods of investigation must be measured. All laboratory methods, by whatever name they may be called, are only makeshifts, because they imitate disease artificially, they can touch only the extraneous aspect of matters. They may show some objects from a different view-point but they will never present the vital point, the origin and development of the functional disturbance, the ingenious compensation as manifested by the struggling organism under peculiar conditions. They can never be identical with the real mechanism and with the nature of regulative processes encountered as symptoms at the bedside. Experiment, correctly undertaken, enriches scientific knowledge, but it must not pretend to be the guide of practical action at the bedside, for it shows only the limits of compensatory capability, not the form of compensation. Much as I acknowledge the value of operative and exploratory proceedings in establishing correct views as to the functional capacity of various organs—I need only mention extirpation of the pancreas—it is well to keep in mind the limits of these methods of observation, and not to be persuaded that in the majority of these cases the test conditions in an experiment, ever so carefully conducted, may in any wise imitate or be a substitute for slowly progressive changes manifested by disturbances of function which are called disease.

FUNCTIONAL DISEASE AND FUNCTIONAL DIAGNOSIS

Rosenbach's work which particularly influenced medicine dates back to his early years. In 1878, when he was only 27, he contributed two papers which, as previously mentioned, inaugurated formally the new trend in internal medicine of thinking of disease in its earliest manifestations when there is still functional disturbance only and before there is structural or organic change. The first paper entitled "The Mechanism of Gastric Insufficiency" was the result of the work he had carried on at Jena under the influence of his former master Leube.

The crux in the diagnosis of gastric function, digestive as well as motor, is not in the determination of the size of the organ, for this furnishes only uncertain and late criteria. When a stomach is so dilated that its size is undoubtedly abnormal, and its digestive function, as indicated by undigested food content, is so definitely impaired as to make the diagnosis simple the best that can be hoped for is an arrest of the process, but not improvement. If we desire to cure we must set ourselves not to make a diagnosis of an irreparable pathologic condition, but rather to recognize early the origin of the affection, the beginning of the process, the *functio laesa* of the organ, and because of this we must lay the main emphasis on functional diagnosis. Medicine as far as possible must free itself from the dominance of the viewpoint of pathological anatomy.

Dilatation of the stomach is not a completed state in the anatomical sense, but rather a gradual process, and we can obtain information on the first stages or milder forms not through anatomical measurement of the size of the organ, but rather through testing physiologically its functions. Just as we cannot reach a conclusion on the strength of the heart from its size, but must consider the tension and quality of the pulse so it is impossible without careful investigation of the efficiency of the stomach to draw a conclusion as to its strength merely through measuring its dilatation.

There is no way of knowing exactly when a stomach is larger than normal. The size of this organ can only be of diagnostic value if it changes under observation. It must be clear then that the stomach will undergo dilatation only when there is a discrepancy between its expelling motor force and an undue resistance. Muscular hypertrophy will compensate for a while the entailed increased work. But as soon as the obstruction is too great or too prolonged, no longer controllable by increased work, there must occur a stretching of the stomach wall through ingested material and the stretched and overburdened muscle fibers get into a more or less parietic state. But this weakness occurs not alone through mechanical stretching but often through coincident nutritional disturbance of the muscles. Incidentally I want to note that such functional disturbance of the gastric musculature of even high degree will only seldom show microscopic changes—the same is true in the case of heart weakness.

Disproportion between expelling motor capacity of the stomach and increased effort-demands leading to its enlargement may be due either to obstruction or to catarrh, or to unusual amount or quality of food hurriedly ingested, in addition there may be the congenital weakness of the stomach wall or that acquired during acute infections and upon the degree of paresis of the stomach will depend the extent of the disability, also it is evident that the instances of stomach dilatation hitherto recognized represent but a late end-result of a series of transitory dilatations. A sharp distinction must be made between functional or relative and permanent or absolute dilatation. A large stomach may be normal while a much smaller one may already

clearly show functional disturbance under certain strain. In other words, dilatation of the stomach depends on the efficiency of the musculature and the extent of excessive resistance. With increase of one or diminution of the other there will intervene an insufficiency of the expelling motor forces, resulting in a relative insufficiency of the stomach. Overstepping the functional limits of the stomach, capable to cope with the ordinary tasks, will result in a relative insufficiency which sooner or later will invariably become absolute. So the center of gravity of diagnosis is not in the size of the stomach but in the functional test of its expelling motor force. It seems better thus to choose the name gastric insufficiency for disease phenomena and to reserve the term dilatation for irreparable, end-results of gastric insufficiency.

What are the methods of making a diagnosis of gastric insufficiency? First there is inquiry into the patient's symptoms due to food and eating habits, also the study of vomitus, if present. Then there is the study of gastric contents by means of the stomach tube according to Leube before and after test meals, or at times after indigestible food such as dried berries has been eaten. Sometimes succussion sounds two or three hours after a test meal may be studied, or the rise and fall of the level of the stomach contents is reflected through a speculum, or through sounds produced in the stomach, through compression with inflatable balloons introduced through the stomach tube, or the contractability of the stomach may be tested by filling and emptying the stomach with water. Through these investigations disturbances of the digestive and motor capacity of the stomach can be determined and measures instituted for their correction through appropriate diet in divided quantities.

So the therapy of gastric insufficiency will depend directly on an early exact diagnosis. And, furthermore, by developing this mode of investigation we may succeed in approximating the diagnosis of diseases of the stomach to that of the chest. To attain this objective we must not, however, shun new methods even though it may at first seem as unnecessary as did percussion and auscultation to our predecessors for we may hope for more happy therapeutic success in diseases of the abdomen because of easier accessibility than in the case of diseases of the chest.

The other paper which appeared in 1878 was entitled "On Experimental Cardiac Valvular Deformities." It was produced under the stimulus of Julius Cohnheim and read as his habilitation thesis when he became privatdozent at Breslau. Working with rabbits and dogs he produced artificially lesions of the heart valves, and found that severe insufficiency and stenosis of the valves could not change the arterial blood pressure, that compensation intervened at once. He attributed this capacity to "the latent reserve force of the heart muscle," a term original with him. "It is, therefore, experimentally established that there is a compensatory mechanism in the heart which can straighten out sudden disturbances in the balance of the circulation." In the same work he attempted also to show when and under what conditions endocarditis may be produced, and to answer what bearing these experiments had on questions of clinical interest.

This concept of insufficiency of organs and a compensatory mechanism through latent reserve force became the "leit-motif" throughout his unusually rich career, and in succeeding years he also described insufficiency of the intestinal tract, and applied this same concept to the kidneys, the nervous system and to disturbance of metabolism such as diabetes and obesity. The physician must not wait until permanent dilatation of the stomach or

heart has occurred or paralysis of the intestines. His aim must be to recognize insufficiency, or the state of disproportion between the demand on an organ and its ability to perform the work. Functional diagnosis must be developed as contrasted with the anatomical form, so that disease may be recognized in its incipency, in the transition from fatigue to actual change in the tissues and organs. A cure may be achieved then by lessening the load on the organ—impossible after permanent changes have set in.

Diagnosis should not be an end in itself nor a means of systematic classification but should at all times aim for a balance of energy, it is the triumph of medical art only when it furnishes a direct basis for prophylaxis and therapy. Medical efficiency is not based on the diagnosis of mitral insufficiency or fatty heart, but on the decision as to what is the cause of the disturbance, on the extent of functional disturbance of valve or muscle, on how strong the compensatory forces are, and under what conditions an early disturbance of balance can be restored.

Diagnosis, then, was to Rosenbach but an instrument for better understanding of life in general, so as to enable the physician to see the human individual as a harmoniously well balanced dynamic organism.

The physician of the future will be compelled to consider, above all, prophylaxis, the rational distribution of the products of internal and external activity—i.e., the correct alternation of rest and labor, the appropriate adaptation to changes of the external conditions of life, and the harmonious development of all physical and mental functions. He will not, in the frame of a formal diagnostic systematism, as a cellular pathologist grasp after symptoms pathognomonic of local changes of tissue, but he will endeavor, as a biologist, to obtain a broad view of the realm of energetics (the province of which is modern organic physiology) and of the total balance of phrenosomatic activity.

HIS PLACE IN THE HISTORY OF MEDICINE

Even the fragmentary bits of his life and work recorded here stamp Ottmar Rosenbach as an extraordinary figure in medicine. Yet how little was he appreciated in life, and how few know him now! Partly, this was due to his nonconformist personality. Celibate, retiring yet unusually generous and understanding and genial in a small circle of friends, finding solace with his heroes Heine, Schiller and Goethe, Schopenhauer, Kant and Spinoza, he was almost eccentric in his devotion to medicine. But he was a keen, prodigious investigator, a great clinician, and a fearless, original thinker. He was not always right, in his great zeal to prevent and cure disease by recognizing it in its incipient stages he often failed to recognize the importance of etiology in disease. Nevertheless his original concepts, worded originally, have become thoroughly integrated in our clinical thought and speech. Especially profound and stimulating in its influence on the development of internal medicine was his concept of functional disease and functional diagnosis. For this he holds a notable place in the history of medicine.

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CASE REPORTS

GENERALIZED ACTINOMYCOSIS, REPORT OF A CASE *

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SINCE Israel's ¹ original paper in 1878 on actinomycosis in man, the disease has been observed with increasing frequency so that it can no longer be considered the rarity it once was. Even as far back as 1899, Ruhrah ² collected 58 cases that were reported in America, and, reviewing the literature, he found a total of 1094 cases. Of these 56 per cent were of the cervico-facial type, 20 per cent gastrointestinal, 15 per cent pulmonary, 2 per cent skin, and 6 per cent were doubtful.

Numerous reports have followed these early contributions, but few indeed have been the cases of generalized actinomycosis. In 1925 Sanford and Voelker ³ reviewed 670 cases of actinomycosis that had been observed up to that time in the United States. Of these, in only 13 was there a generalized involvement. In 1925 Werthemann ⁴ collected four cases of actinomycosis with generalization and added two of his own. A number of other reports have appeared in the literature, notably those of Becker, ⁵ Schinz and Blangey, ⁶ Shapiro, ⁷ Kasper and Pinner, ⁸ Fried and Light, ⁹ Fellingner and Salzer, ¹⁰ and others.

Despite the fact that the generalized form has been reported in the literature in a number of instances, this type of actinomycosis is still rare enough and of sufficient interest to warrant the addition of another case, particularly so since the diagnosis was made ante-mortem.

CASE REPORT

Clinical History J C, a white male laborer, aged 47, was admitted to Sea View Hospital June 27, 1936. In February 1936, the patient had developed cough, expectoration, and fever. The cough, moderately severe in character, persisted for several weeks. It then abated somewhat, but a slight cough continued. In April a tender red swelling appeared on the lateral surface of the right lower leg. This was incised, but failed to heal, and continued to drain a thick greenish-yellow pus. In the latter part of April, the cough and expectoration became much worse and on one or two occasions he expectorated a little blood. In May an abscess appeared on the left arm and a week later another abscess developed over the right buttock. In the latter part of May 1936, the patient developed constant dull pain in the right lumbar region associated with chills, sweats, frequency, urgency, nocturia, burning on urination, and a temperature ranging between 102 and 104°. On June 16, 1936 he was admitted to a City General Hospital. There, the abscesses over the buttock and left arm were incised, but continued to drain. Because of the pulmonary symptoms, and because of a chest plate showing a density at the right apex, a diagnosis of pulmonary tuber-

* Received for publication February 26, 1937

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culosis and possible right pyelonephritis was made and the patient was transferred to Sea View.

Physical Examination On admission to Sea View Hospital, physical examination revealed a poorly nourished adult male who appeared acutely ill. The teeth were carious. There were impaired resonance and diminished breath sounds at the apex of the right lung. The blood pressure was 114 systolic and 70 diastolic. The heart and abdomen were negative. There was an ulcer on the left arm about one inch in diameter from which a small amount of greenish-yellow pus exuded. The skin margins of the ulcer showed a reddish-purple discoloration, and the surrounding tissue was indurated. A similar ulcer, about two inches in diameter, was seen over the right buttock, and a third was noted on the right lower leg. There was an exquisitely tender swelling in the right lumbar region and the Murphy sign was positive.

Laboratory Findings The sputum was persistently negative for tubercle bacilli. The urine was clear, specific gravity 1.018, albumin one plus. It showed, microscopically, many clumps of white cells, a few red blood cells, and occasional granular casts. The blood hemoglobin was 51 per cent. There were 2,820,000 red blood cells and 16,800 white blood cells. The differential smear showed 88 per cent polymorphonuclear leukocytes, 6 per cent lymphocytes, and 6 per cent monocytes. The blood chemistry was normal. Blood cultures were negative. The sedimentation rate was 115 mm in 45 minutes. The Wassermann test was negative.

Roentgen-Ray The posterior anterior view of the chest showed an opacity in the region of the right apex. This was interpreted as being due to a thickened pleura (Figure 1). Roentgenograms of the bones underlying the cutaneous ulcers showed no evidence of bone involvement. The spine was negative.

Course The temperature was hectic in character, and ranged between 98 and 102°. The pulse rate was 80 to 100. Frequency, urgency, and right lumbar pain were prominent symptoms. On June 30, he developed severe persistent frontal headache. The next day the patient vomited twice. Neurological examination on July 2, 1936 revealed nuchal rigidity and positive Kernig and Brudzinski signs. The cranial nerves were not involved. The deep reflexes were bilaterally markedly exaggerated, and ankle clonus was present. There was a suggestive Hoffman sign on the left, but the other pathologic reflexes were negative. Bilateral choked discs were seen. The spinal fluid was clear and the pressure was 10 millimeters of mercury. The Pandy was positive. There were 320 cells predominantly lymphocytes. The spinal fluid sugar was 37 mg and the chlorides were 610 mg. On July 3, the patient was comatose. Neurological examination at this time showed in addition to the previous findings, bilateral positive Babinski signs. A spinal puncture was again done. The fluid was under increased pressure, cloudy, and contained 1900 cells per cubic millimeter of which 95 per cent were polymorphonuclear leukocytes. On the same morning an aspirating needle was inserted into the swelling in the right lumbar region and 20 c.c. of thick greenish-yellow, very foul smelling pus were removed. On more careful examination of the pus numerous small yellow granules were observed. These granules, when crushed under a cover slip and examined microscopically, were found to consist of mycelial threads with clubbed ends. The patient died at 5 p.m. on July 3, 1936.

The clinical diagnosis was Pyemic form of actinomycosis, multiple actinomycotic brain abscesses and meningitis, actinomycotic perinephritic abscess, multiple actinomycotic abscesses of the skin.

Necropsy The necropsy was performed 16 hours after death. The body was that of an emaciated adult white male. The subcutaneous ulcers previously described were observed on the upper portion of the left arm on its lateral surface, over the right buttock, and over the external malleolus of the right leg. The underlying bones were not involved.

The right lung was firmly adherent at the apex to the chest wall. The left lung was free. The pleurae over the apex of the right lung were adherent and thickened, measuring 2 cm in thickness. In the apex of the right upper lobe, the lung tissue for a distance of 1.5 cm from the pleura was firm, flat, grayish-black in appearance, and non-resilient. Just beneath this area and under the lateral pleura there was an emphysematous bleb measuring 1 cm in diameter. The lung tissue of the right middle lobe was well aerated for the most part. Situated just above the interlobar fissure



FIG 1 Roentgenogram of chest showing an opacity at the right apex. At autopsy this opacity was found to be due to a non-specific fibrosis. The primary actinomycotic lesion found at autopsy in the right middle lobe is not visualized.

and 6 cm from the lateral pleura, there was a soft yellow mass 1 cm in diameter. This was well encapsulated (figure 2). There was no change in either of the lower lobes. An emphysematous bleb measuring 2 cm in diameter was seen just beneath the apex of the left upper lobe. The tracheobronchial nodes were enlarged.

Surrounding the right kidney there was a large abscess cavity measuring 10 cm in diameter. This was filled with thick putrid yellow-green pus. In the posterior portion of the kidney substance near its upper pole there was an irregular soft yellow mass measuring 6 cm in its longest diameter. This was composed of necrotic and

purulent material. It communicated with the previously described large abscess and also with the renal pelvis (figure 3). A small amount of pus was present in the right renal pelvis and ureter.



FIG. 2. Gross specimen of right lung showing small primary actinomycotic focus in middle lobe.

On opening the dura, a small amount of thick green pus was seen over the occipital and right frontal regions. The meninges were markedly congested. In the anterior portion of the right frontal lobe two abscess cavities filled with greenish-yellow pus were noted. The larger measured 2 cm and the smaller 1.5 cm in diameter. A similar abscess 1 cm in diameter was found in the right parietal lobe and another in the cortex of the left occipital lobe (figure 4).

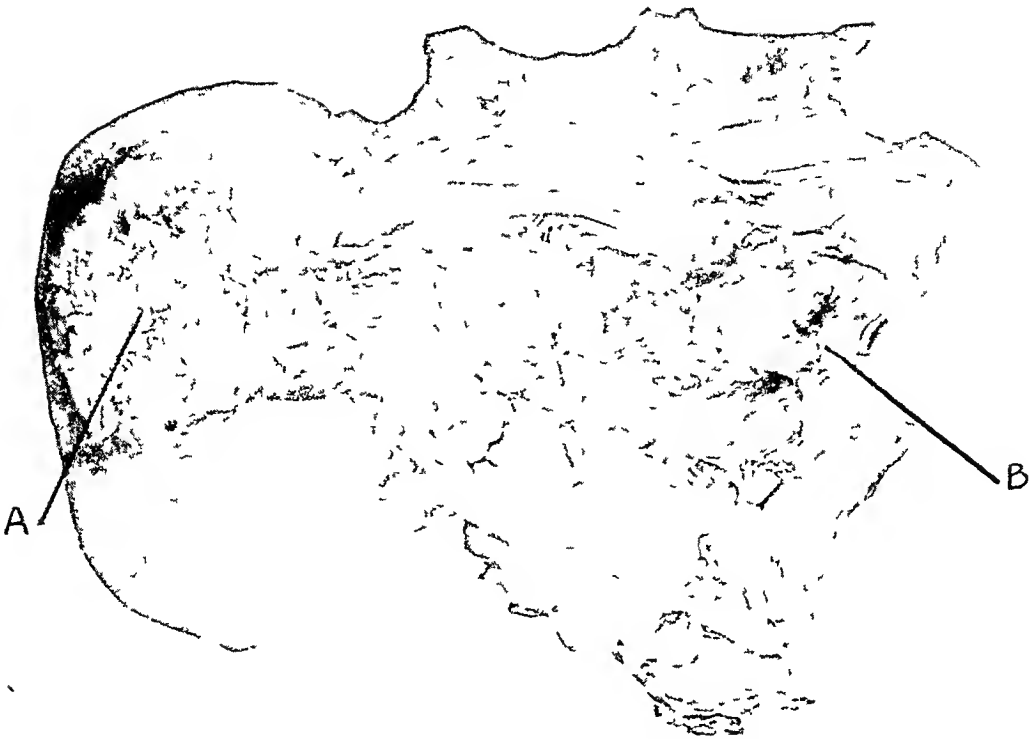


FIG 3 Actinomycotic abscess (A) in kidney substance and (B) perinephritic abscess



FIG 4 Section of brain through occipital lobe showing actinomycotic abscess

Histopathology

Lung In the section of lung through the small yellow mass described grossly, there was an abscess composed of a dense accumulation of polymorphonuclear leukocytes with a few lymphocytes and large mononuclear cells. At the periphery of this abscess a ray fungus was seen. This consisted of a central granular mass with peripheral club formation. In the Gram stain, the central mass was seen to consist of branching mycelial threads. The abscess was surrounded by granulation tissue composed of epithelioid cells, fibroblasts, lymphocytes, and collagen fibers.

Kidney In the section of kidney there was an abscess composed of polymorphonuclear leukocytes, nuclear remnants, lymphocytes, and large mononuclear cells. Several ray fungi were seen (figure 5). These were similar in character to those described in the lung. The wall surrounding the abscess was larger in diameter than



FIG. 5. High power section through kidney abscess showing ray fungus.

that seen in the lung and was composed of lymphocytes, epithelioid cells, and polymorphonuclear leukocytes. Very little fibrous tissue was seen.

Brain Abscess In this section an abscess was seen which was composed chiefly of polymorphonuclear leukocytes, but also of lymphocytes, and nuclear remnants. Occasional ray fungi were present. The wall of the abscess contained epithelioid cells, lymphocytes, fibroblasts, large mononuclear cells, and a few polymorphonuclear leukocytes. Within the cytoplasm of the large mononuclear cells fat droplets and necrobiotic nuclei were observed. Collagen fibers were present in moderate amount at the periphery of the wall of the abscess. In the leptomeninges the blood vessels were engorged and there was a dense infiltration of lymphocytes, large mononuclear cells, and occasional polymorphonuclear leukocytes.

Skin Ulcer In the corium as well as in the subcutaneous tissue there was a collection of lymphocytes, mononuclear cells, epithelioid cells, fibroblasts, and a few polymorphonuclear leukocytes. The capillaries were engorged.

Anatomic Diagnosis Primary actinomycosis of the right middle lobe of the lung, generalized actinomycosis with actinomycotic abscesses in the brain, right kidney, and skin, actinomycotic meningitis, actinomycotic right perinephritic abscess, fibrosis of the apex of the right lung (non-specific), emphysematous blebs in both lungs, dilatation of the heart, diverticulum of the rectum

COMMENT

For many years the dispute over the etiology of actinomycosis revolved itself around the question as to whether the organism was the anaerobic one of Wolf-Israel¹¹ or the aerobic one of Bostroem¹². Bostroem's organism is exogenous and is found widely distributed on grain and plants. The Wolf-Israel type is anaerobic, grows at a temperature of 37 degrees and will not grow at room temperature. Wright¹³ obtained cultures of the anaerobic organism from clinical cases of actinomycosis and concurred with Wolf-Israel in their conclusion that the anaerobic organism was the etiologic agent. In 1910 Lord^{14, 15} found organisms with the morphological and staining reaction of actinomyces in carious teeth and in tonsillar crypts of normal individuals. When this material was injected intraperitoneally into guinea pigs, it gave rise to tumors which histologically were similar to actinomycotic tissue. He concluded that the buccal cavity was a normal habitat of actinomyces and was the source of infection. As a result of this work the previously widely accepted conception that chewing infected grain or straw led to actinomycosis was quite generally abandoned, and the aerobic organisms were considered entirely saprophytic.

Naeslund¹⁶ after extensive investigation with various strains of both aerobic and anaerobic organisms has found that there are pathogenic and non-pathogenic strains of each type. He thus divides the pathogenic actinomyces into two groups, actinomyces-alpha and actinomyces-beta and gives the following characteristics for each.

Actinomyces-alpha Found in the mouth and gastrointestinal tract of normal individuals and not found free in nature. It is chiefly anaerobic, grows best at body temperature, and little or not at all at room temperature. It is rarely acid fast, never forms spores, and shows little resistance to drying. It forms long threads and clubs in the body and usually shorter rods on artificial media. Growth on agar is very slight. It is quite pathogenic for cattle but only slightly so for guinea pigs and rabbits. Its portal of entry in the human body is the mucous membrane of the mouth and intestines, and less often the lungs. It usually produces actinomycosis of the cervico-facial type and of the gastrointestinal type and rarely of the lung. Spread of the disease occurs by direct extension. Generalization through the blood stream is rare. The clinical course is, as a rule, mild. There is little or no fever and the prognosis with treatment is good.

Actinomyces-beta Found free in nature, is aerobic, and grows well on agar at room temperature. Spore formation is common. It forms long threads in the body and on media, but club formation is not common. It strongly resists drying. It is quite pathogenic for guinea pigs and rabbits and less so for cattle. The portal of entry in the body is usually the lung and less often the skin. The fungus reaches the lung either by means of inhalation or by aspiration from the mouth. It, as a rule, produces actinomycosis of the lungs and

spreads by direct extension and by metastases through the blood stream. The course of the disease is relatively rapid and usually fatal.

The two types, however, can not be too sharply demarcated since cases have been reported in which the organism could be grown both aerobically and anaerobically (Naeslund,¹⁶ Fellingner and Salzer¹⁰).

In our case, we were unsuccessful in obtaining a pure culture although numerous attempts were made under both aerobic and anaerobic conditions and with several types of media.

The primary lesion in the generalized form of actinomycosis is, in the very large majority of instances, located in the lung. In a review of 20 cases described in the literature and including our own, the primary lesion was in the lung in 15, in the cervico-facial region in two, and in three it was doubtful. Although the lower lobe is usually the seat of the focus, it not uncommonly is seen in the upper lobe.

The size of the primary lesion as observed at autopsy varies greatly. It may be very small, in fact, so small that it can be missed entirely unless carefully searched for. In our case the small focus was not found at autopsy until the second examination of the lungs was made. Even the roentgen-ray plate of the chest, perhaps because of the anatomic location of the nodule, did not reveal evidence of its presence. It is extremely important to keep this fact in mind. Several cases of primary actinomycosis of the brain have been reported (Howard¹⁷) although it is most difficult to explain how this organ can be the primary seat of the disease. As Jacoby¹⁸ points out, it is quite possible that in these cases, either the true primary lesion was missed by the pathologist, or else the patient had a small primary lesion during life which was not observed by the physician and subsequently healed. The evidence for the conclusion that the pulmonary lesion was the primary one in our case is that, in the first place the pulmonary symptoms were the first to appear, and secondly, the anatomic character of the lesion observed at autopsy indicated that it was the oldest in the body.

The primary lesion can and very frequently does spread by direct extension to involve a large portion or the entire lung. It may extend by continuity to the pleura producing an empyema, into the chest wall with the formation of an abscess, and into the pericardium and myocardium. Progression by way of the lymphatics is denied by most authors. The lymph nodes are usually enlarged and edematous, but rarely show evidence of the actinomycotic process. In a case reported by Werthemann,⁴ however, the tracheo-bronchial glands were definitely involved. Generalization by way of the blood stream in instances of primary actinomycosis of the lung does not appear to be very uncommon. The organisms invade branches of the pulmonary veins and thus enter the general circulation. Kasper and Pinner⁸ and Fellingner and Salzer¹⁰ both demonstrate beautiful histological sections which show the ray fungi within the pulmonary veins.

Metastases may be wide spread, involving many organs, or they may be very few in number. The brain was the most common location for metastases in the cases reviewed, being affected in 15 of the 20 cases. In the order of decreasing frequency, metastases occurred in the kidneys, the skin and subcutaneous tissue, the spleen, the lungs, the heart, the liver, the bones, the thyroid,

the intestinal wall, the lymph nodes, and the testicle. There were three perinephritic abscesses in the 20 cases. It is interesting to note that metastatic involvement was greater in those instances in which there was involvement of the heart.

When the brain is affected metastatically in generalized actinomycosis, abscess formation is the most frequent type of lesion. There may be one or several abscesses, and there appears to be no predilection for a particular lobe. The meninges can be secondarily involved. Abscess formation was present in 13 of the cases reviewed. In one (Fellinger and Salzer¹⁰) a subarachnoid granuloma was seen, and in another (Snook¹⁹) the meninges alone were involved. This is contrary to the findings noted in actinomycosis of the central nervous system resulting from direct extension of an aural lesion. In these, meningitis is frequent and abscess formation less common (Moersch²⁰).

The heart and pericardium may be involved by direct extension or by the hematogenous route. When the blood stream is the avenue of approach, numerous small abscesses are found in the myocardium. One of these may break into a chamber of the heart and thus provide a second source of dissemination. When the spleen, liver, thyroid, intestine, and lungs are affected secondarily, many small abscesses are generally found. In the intestine they are seen within the wall. The kidneys may show multiple small abscesses or there may be a single large abscess in the cortex of one kidney which extends into the pelvis, or peripherally, giving rise to a perinephritic abscess. Bone can be invaded by direct extension from a neighboring organ, but in most instances actinomycosis of the skeletal system is the result of a hematogenous spread. Even the mandible which is so close to the most frequent site of actinomycosis, the cervicofacial region, is rarely invaded by direct extension (Kaufmann²¹). The spine is the most common of the bones affected. There are sharply defined abscesses, as a rule present in two or more vertebrae. The bodies, pedicles, and laminae are attacked, but the intervertebral discs are usually spared. A marked destruction of the vertebral bodies may occur without collapse or kyphosis (Tabb and Tucker²²).

It is beyond the scope of this paper to discuss at any length the varied and bizarre symptoms that can occur in a pyemic disease of this kind. The symptomatology will, of course, depend upon the organs affected and the extent of disease in these organs. Before generalization has occurred the symptoms are those of the primary lesion. If it be in the lung, as it usually is in these cases, then the severity of the symptoms will usually be proportional to the extent of the lesion. Cough and expectoration of sputum which is occasionally blood streaked are prominent complaints. Pain in the chest, night sweats, fever, and loss of weight are not unusual. The sputum may be thick, copious, and fetid, or it may be scanty and odorless (Christison and Warwick²³). Once generalization has occurred, the symptoms referable to other organs affected may be so prominent that they completely overshadow those of the primary lesion and one has to question the patient carefully to learn the nature of the onset of the illness.

The temperature is hectic, usually ranging between 98 and 102 degrees. The pulse rate is proportional unless there is cerebral involvement with increased intracranial pressure. Chills and sweats are frequent. The white blood cell count ranged between 10,400 and 19,600 in those cases in which it was reported.

The differential counts showed between 82 and 88 per cent polymorphonuclear leukocytes and 12 to 18 per cent lymphocytes. Moderate secondary anemia is usually present.

Perhaps the most important factor in the diagnosis is to remember that this disease, although extremely rare, does exist. It should be considered in all pyemias whose origin and nature are not apparent. The duration of the entire illness in the cases reviewed ranged between three months and two years. However, it was not always possible to determine from the histories given approximately when generalization had occurred. It is likely that most patients live but a few months after metastases are evident.

A careful search of the sputum should be made when the disease is suspected. If sulfur granules are present and these, on microscopic examination, show the mycelia, the diagnosis is definite. It is not sufficient to culture a routine sputum specimen for fungi. As was mentioned before, actinomyces have been found in the mouths of normal individuals, and a positive culture may readily lead to error.

A careful examination of pus obtained from secondary foci may lead to the diagnosis as it did in our case. This, of course, is not always possible. Biopsy examination is indicated whenever it can be done. Blood cultures have been almost uniformly negative. Fellingner and Salzer¹⁰ obtained a culture from the postmortem blood which was pathogenic for laboratory animals. Freed and Light⁹ claim that they obtained four aerobic cultures in their case during life, but no attempt was made to produce the disease in animals.

Attempts have been made to develop an intradermal reaction as a diagnostic test in actinomycosis, but the results thus far have been controversial and discouraging. De Area-Leao²⁴ reported distinct cutaneous reactions in two cases of actinomycosis when 0.3 c.c. of a filtrate from an old broth culture of *actinomyces bovis* was injected intradermally. Normal individuals gave no reaction to such injections, and control injections of sterile broth also failed to give positive results. Adant and Spehl²⁵ also obtained positive intradermal reactions in two cases of pleuro-pulmonary actinomycosis by using a filtrate of an old culture of *actinomyces bovis*. The reaction appeared 12 hours after injection, was characterized by erythema, an indurated zone 2 to 3 cm. in diameter, and disappeared in four or five days. They also obtained negative results in normal individuals, but did observe positive reactions in patients having other types of mycotic infections. They concluded that a positive reaction was indicative of a mycotic process in the body, but was not specific for actinomycosis. On the other hand, Mathieson, Harrison, Hammond, and Henrici²⁶ found that normal individuals gave more frequent and more marked skin tests to *actinomyces bovis* than did actinomycotic patients.

SUMMARY AND CONCLUSIONS

A case of the generalized form of actinomycosis has been presented. The primary lesion is, in most instances, in the lung. Metastases may be wide spread or few in number. The brain is the most frequent organ secondarily involved. The symptoms are varied depending upon the organs affected.

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ABNORMAL SENSITIVITY TO LIGHT IN A CASE OF POSSIBLE
LANDRY'S PARALYSIS¹By H F BLUM and I C SCHUMACHER, F A C P, *Berkeley, California*

THE purpose of this report is to describe a condition of acute hypersensitivity to light occurring in a patient during the earlier stages of a fatal ascending paralysis resembling the type described as Landry's syndrome, and to discuss the relationship of this condition to other types of photosensitivity. The patient remained in the hospital for a period of two weeks, during which time it was possible to make a rough characterization of her sensitivity to light. No definite diagnosis of her condition was made at the time, although certain neurological changes were observed. A few days after returning to her home in a nearby city, acute dementia and marked paralysis—first of the feet, then of the legs, and on up—developed, and she died on February 17, 1935. No autopsy was performed, but the clinical diagnosis made by the attending physician was Landry's paralysis.

When first observed in the hospital, the patient displayed a fiery erythematous dermatitis on the face, hands and arms. The delimitation of this dermatitis was such as to suggest that it was the result of exposure to light, only the face, hands and arms were affected and these only on the parts which would be most exposed to sunlight. The submental triangle, and the interior surfaces of the hands and arms which would ordinarily be shielded from light showed little or none of the erythema. A very striking demarcation existed between the erythematous exterior surfaces of the hands and arms, and the more or less normal medial surfaces, this is shown in the photograph reproduced as figure 1, which was taken after the patient had been in the hospital for two weeks protected from direct sunlight, and the erythema had begun to fade. The dermatitis was more noticeable on the lower arms and the hands than on the upper arms, as though the periods of exposure had been different due to the wearing of different sleeve lengths. No trace of the dermatitis appeared on any portion of the body which might not have been exposed to light under ordinary circumstances. The answers of the patient to questions regarding exposure to sun were not trustworthy, at one time she denied having been recently exposed directly to sunlight, but at other times stated that she had been so exposed. The following is a summary of the history, physical, and laboratory findings other than sensitivity to light.

CASE REPORT

G K, a 40-year-old white American housewife, was admitted to the University of California Hospital on January 6, 1935.

Chief Complaints Swelling of the face, with a burning, itching eruption of the face, hands and arms, progressive weakness, and vomiting.

Family History The maternal grandfather died of cardiac disease, and the maternal grandmother of renal disease. No history of tuberculosis in the family was obtained.

* Received for publication March 1, 1937.

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Assisted by a grant from the Research Funds of the University of California.

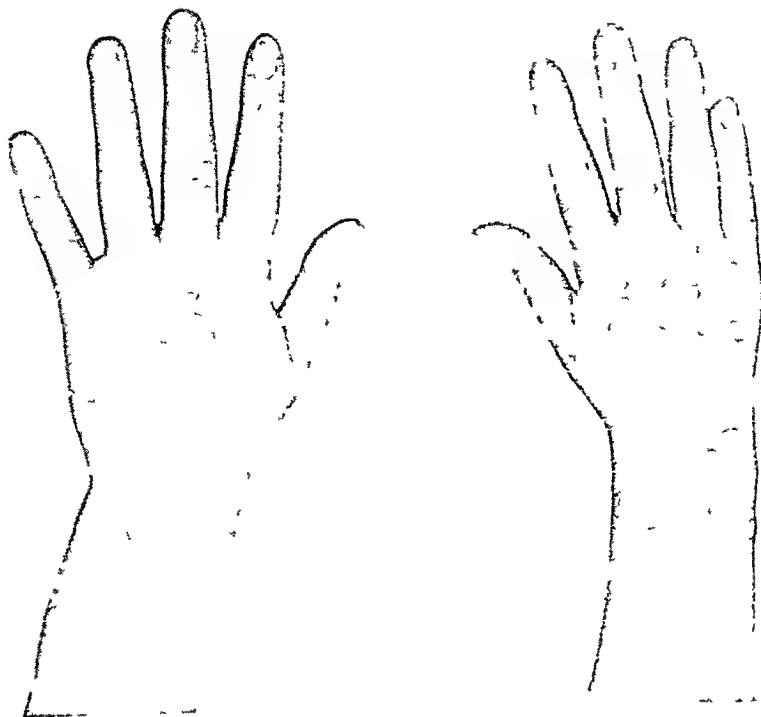


FIG 1

Marital History The patient had been married for 21 years. Her husband was living and well, age 41. Two children, ages 7 and 19 respectively, were living and well. There had been no miscarriages or abortions.

Past History The patient had pneumonia at the age of 12, and again when she was 39 years old. She had scarlet fever when she was 21 years old, and at the same age, when her first child was born, she was confined to bed for several weeks with fever, pleurisy and hemoptysis. Tonsillectomy and appendectomy were performed at the age of 28. At the age of 30, she was confined to bed for two months because of shortness of breath and tachycardia. Cholecystectomy was performed when she was 28 years old, for cholecystitis and cholelithiasis, recovery was uncomplicated.

Menstrual history was negative except for two periods missed between October and December 1934.

The patient has been obese since the age of 27, average weight, 225 pounds. Her weight reached a maximum of 250 pounds when she was 34 years old. At the time of admission to the hospital she weighed 216 pounds.

Present illness began with a sore throat and fever in October 1934, three months prior to entry. This was followed in two days by generalized muscular tenderness and soreness. The patient went to bed, and remained in bed until she entered the hospital. A week after the onset of illness she was seen by the family physician, and quinine in capsules was prescribed. Several days later, after she had taken 12 of these, an eruption appeared—first on the cheeks, then on the hands, arms and legs, and eventually over the entire body. This eruption consisted of minute red areas, which later coalesced to form purpuric patches. The quinine was discontinued, and sodium salicylate was given by mouth. Her fever gradually subsided. Marked swelling of the face with brawny induration appeared, later extending to the dorsum of the hands and forearms.

After one month the brawny induration and eruption of the skin had disappeared except that of the face, an exposed area of the chest not covered by her nightgown, and the extensor surfaces of the hands and fingers. These areas felt hot to touch, although the patient had no fever at this time. Parts of the skin not exposed to light showed no discoloration. One month after the onset of illness, heavy traces of albumin appeared in the urine, and were present there for one month during which time the patient's legs and forearms were quite noticeably swollen. This edema subsided as the albuminuria disappeared.

Shortly after the onset of her illness, the patient noticed weakness of the extremities, especially of the legs. This weakness progressed until, at the time of entry into the hospital, she was unable to rise from a sitting position.

Six weeks prior to entry, the patient began to have attacks of vomiting, which occurred usually in the mornings after breakfast, later, though not frequently, at other times of the day. Her appetite became poor, but loss in weight was slight. A study of her dietary habits previous to her present illness revealed no outstanding deficiency. During her illness previous to entry, her diet had consisted mainly of citrus fruits with the occasional addition of toast and cereal. For three weeks before entry, all medication was withheld without causing relief of her symptoms, and darkening of the patient's bedroom had no appreciable effect on the skin lesions.

Physical examination showed an obese woman, lying in bed in no apparent distress. The appearance of the skin has been described elsewhere. The heart and lungs were negative. Pulse was regular in force, rhythm 120 per minute. Blood pressure with the patient prone was 150 mm of mercury systolic, and 95 mm diastolic. The abdomen was very obese, and covered with numerous striae. An upper right rectus scar was present, and an old appendectomy scar. No abdominal organs or masses could be palpated. Pelvic examination showed an irregular, torn cervix, and the presence of a leukorrheal discharge. Rectal examination was negative. There was muscular weakness in all extremities, and the muscles were flabby. Arm reflexes were present but hypoactive. Knee jerks could not be obtained. Ankle jerks were present. Plantar response was normal. There was reduced sensitivity to pinprick over the medial aspects of both legs from the knee to the ankle, as well as over both deltoid regions and the upper outer chest. The reactions to heat, cold and vibration were normal.

Laboratory Tests

Urine Dark brown to brick-red in color, acid, sp gr 1.030 to 1.041. Albumin faintest possible trace, to negative. Reducing bodies absent. Acetone negative. Sediment (uncatheterized specimen) showed 20 pus cells per high dry field, no casts, no red blood cells. Spectroscopic test for hematoporphyrin negative.

Stool No occult blood, no parasites.

Blood Hemoglobin (Sahli) 85 per cent (12.3 gm), red blood cells 4.05 to 4.65 million per cu mm, white blood cells 7,200 to 5,550 per cu mm. Differential count: PMN 58 to 70 per cent, PME 0 to 5 per cent, PMB 0 to 1 per cent, lymphocytes 20 to 21 per cent, and monocytes 20 to 16 per cent. The red blood cells showed slight anisocytosis and poikilocytosis. Platelets appeared normal in number.

Blood Kahn and Kolmer quantitative test negative. Non-protein nitrogen 30.8 mg per cent. Creatinine 1.3 mg per cent.

Gastric analysis Free hydrochloric acid present.

Basal metabolic rate Plus 24 per cent (probably inaccurate as patient was restless and uncooperative).

Tuberculin skin test Negative to 1 cc of 1:1000 human.

Electrocardiogram (interpreted by Dr. Wm. J. Kerr) showed a rate of 103 per minute, regular rhythm, left ventricular preponderance, slurred QRS complexes.

Roentgen-ray examination of the chest (by Dr R S Stone)—films and fluoroscopy The heart appeared to be enlarged transversely The lungs appeared clear The spleen could not be seen under the fluoroscope

Course The patient was placed on a diet of 1,200 calories Sodium amytal and later chloral hydrate were administered for sleeplessness Massage and passive exercise of all extremities were given During the first four days there were slight daily elevations in temperature, the highest being to 37.7°C on the day of entry, throughout the remainder of her stay in the hospital, the patient's temperature was usually normal, occasionally rising to 37.5°C Her pulse varied between 80 and 120 per minute Vomiting occurred on only a few occasions, chiefly when she was disturbed by diagnostic procedures

Throughout her stay in the hospital, no apparent change occurred in the patient's general condition She remained irritable and uncooperative, and was somewhat resistant to all examinations Details of the diagnostic studies made to determine the etiology of the skin lesions are described below The patient was discharged from the hospital on January 23, 1935

Subsequent course The following information was received from her family physician "About four or five days after returning home, the patient began to complain of increasing weakness in both limbs below the knees, together with recurrent attacks of vomiting A flaccid paralysis set in, involving first the feet, then the legs, thighs, body muscles, upper extremities, and finally the muscles of deglutition The patient became delirious, her temperature rose rapidly, and she died on February 17, 1935 No autopsy was obtained

"At no time did she complain of any pain, there were no convulsive seizures or muscle spasms, nor was there any incontinence, urinary or fecal

"The diagnosis made by the consulting neurologist was Landry's ascending paralysis"

EXPERIMENTAL

Reproduction of the Lesions by Quartz-Mercury Arc Radiation On a number of occasions small areas of the skin of the thighs were subjected to the radiation from a quartz-mercury arc in doses which were estimated as capable of producing only a very mild erythema in normal skin The patient always responded to this treatment with erythema much more severe, and much more persistent than that produced in normal individuals by similar doses, and in the course of a few days the irradiated areas developed the appearance of the erythematous dermatitis which covered her face, arms and hands We will describe a single controlled experiment An area of the skin of the thigh, about 5 cm square, was exposed to the radiation from a quartz-mercury arc of the Hanovia Alpine Sun type, for a period of three minutes at a distance of 20 inches To serve as a control, a light complexioned, healthy individual was given a like exposure, at the same time Within a few hours the normal individual developed a very mild erythema of the irradiated area, which faded in the course of the following day and on the second day could be no longer detected The patient developed an erythema at about the same time as the control, but which, in contrast, increased in intensity for several days On the second day following the irradiation the patient showed a bright red erythema of the irradiated area, at which time the control exhibited no further traces of reaction to the exposure Three days later the exposed area was still bright red and showed a slight scaling, it resembled very closely the erythematous dermatitis exhibited by the face and arms This erythema persisted until the patient

left the hospital 11 days following the irradiation, at which time it was beginning to fade. Another area irradiated two days previous to the above still showed erythema at the end of 13 days, and was beginning to exhibit definite signs of pigmentation at that time.

One area which was given a number of successive irradiations developed a somewhat less severe erythema than the others. The explanation of this is difficult, but it is possible, since this experiment was performed somewhat later than any of the others, that the patient's sensitivity was beginning to decline.

We feel that in these experiments we have reproduced the lesions which this patient displayed on entering the hospital by relatively mild exposure to quartz-mercury arc radiation, her response to such radiation being much more severe and persistent than that of normal individuals.

Delimitation of the Wave Lengths Producing the Erythema The importance of determining what wave lengths produce abnormal sensitivity to light has been stressed elsewhere by the writer (Blum, 1933, Blum et al., 1935). Such a study provides the possibility of deciding whether the abnormal sensitivity is due to a hyperactivity of the normal photodermal mechanism, or is due to the activity of an abnormal photosensitizing substance as is the case in *vitiligo solare* (see Blum, Allington and West, 1935). To determine which part of the mercury arc spectrum was active in producing the erythematous reaction described above, we exposed five areas on the thigh simultaneously to the same dose of quartz-mercury arc radiation used in the experiment described above, one of these areas was exposed directly to the full radiation of the arc, while the other four were covered by glass filters of different spectral transmissions (774, W G, 385, 038, figure 2). A severe erythema of the type described above developed on the area exposed directly to the arc, but no changes were detected on any of the areas covered by the filters. On a later occasion fresh areas were covered with the filters and exposed to the arc for a period of 15 minutes, but again no changes were observed, an exposure of this duration to the direct arc should produce a severe burn in a normal individual.

The curve N E in figure 2 shows the relative effectiveness of various wave lengths in eliciting erythematous response from normal skin, from which it will be seen that no wave lengths greater than 3200 Å are effective. The filter transmissions are also shown in this figure, and it will be seen that any of the filters used above (774, W G, 385, 038), which prevented the production of the abnormal erythematous response in our patient, will also prevent the production of erythema in normal skin, since all remove the radiation shorter than 3200 Å, except 774 which permits only a very slight fraction of the erythemal radiation to pass. On another occasion an area was irradiated through filter 970 for a period of three minutes, with the result that a milder erythema developed than that produced by the full arc although more severe than that which would be elicited from normal skin by such a dose. Figure 2 shows that this filter permits only a part of the normal erythemal radiation to pass, so that the effectiveness of the dose should be considerably decreased.

These experimental facts lead to the conclusion that the wave lengths which produce the abnormal erythematous response in our patient are the same as those which produce erythema in normal individuals. While we cannot rule out the possibility of an abnormal photosensitizing substance having its ab-

sorption spectrum in the same region as that of the substance responsible for normal erythema, it would seem reasonable to neglect this rather vague hypothesis and assume that the abnormal sensitivity of our patient represents a hyperactivity of some part of the normal photodermal mechanism

A much more careful analysis of the spectral sensitivity would be required to give complete justification to this last assumption, but such an analysis would require considerable time and equipment and would not be feasible as a rule when such cases come to observation. On the other hand, the equipment used in the above experiments should be available in any hospital. If a set of filters of known spectral transmissions is not at hand a great deal may be learned by

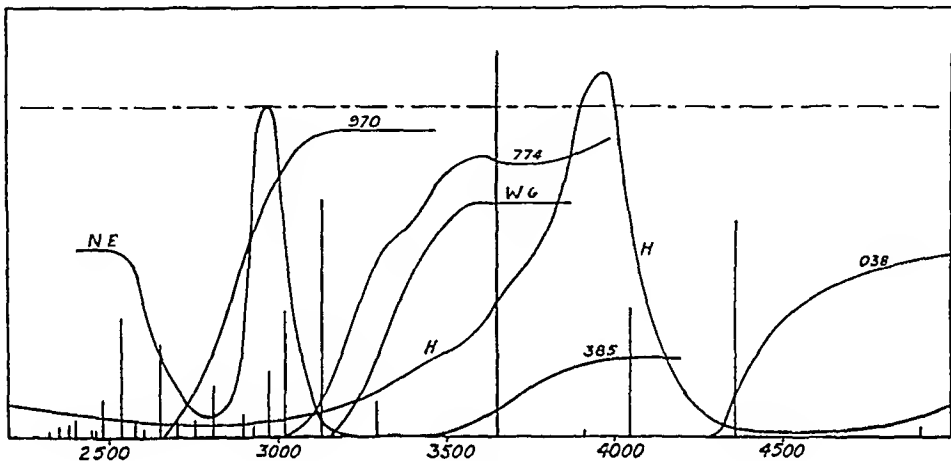


FIG 2

Abscissa—wave lengths in Angstrom units

Ordinates—arbitrary values

NE—normal erythemic response (after Coblenz and Stair, 1934)

H—absorption of hematoporphyrin (values of ϵ calculated from Clar and Haurowitz, 1933)

970, 774, 385, 038—transmissions of Corning glass filters characterized by these numbers
 W G—transmission of a window glass filter. The broken line represents 100 per cent transmission of the filters. The transmission of filter 038 was determined by means of a spectrophotometer, the transmission of the other filters was determined by means of a quartz spectrograph

Vertical lines—the principal emission lines of the quartz-mercury are in this region. The height of the line is proportional to the intensity (data from McAlister, 1933, for a quartz-mercury arc operated at 150 V, 45 A)

using a single filter consisting of a piece of ordinary window glass. The common window glass which appears green when viewed edge on is of fairly uniform spectral transmittency, cutting off the shorter wave lengths at approximately the point where the photo-sensitivity of normal skin ends, i.e., about 3200 Å (see figure 2). If the lesions may be reproduced by radiations passing through window glass, an abnormal photosensitizer may be assumed to be present. If, as in the present case, the patient is hypersensitive to direct quartz-mercury arc radiation but not to that part of such radiation which passes through window glass a hypersensitivity of the normal photodermal mechanism is probably involved. If window glass or any other filters are used in such tests their spectral transmission should be carefully determined. This may be very

well accomplished after the completion of the experiments, as happens to have been done in the present case, thus no time need be lost in making the observations

Since in the present study the lesions were reproduced by quartz-mercury arc radiation, it did not appear important to examine carefully the effects of the spectrum not emitted by this source, the principal lines of which are shown in figure 2 (only a part of the visible spectrum is shown in the figure, the remainder being of no particular interest to the present study) However, an area of the patient's back was exposed to direct sunlight for a period of 20 minutes on one occasion, but without eliciting any skin changes Sunlight does not as a rule contain enough radiation shorter than 3200 Å to produce erythema in normal skin in this period of time, but the quantity of nearer ultraviolet and visible radiation is many times greater than that obtained from the mercury arc

All of the experimental results are summarized in table 1

TABLE I

Source	Exposure time	Filter	Wave lengths transmitted by filter†	Response
Quartz-mercury arc*	3 min	None	All	Severe erythema‡
" " "	3 min	970	2600 and longer	Mild erythema
" " "	15 min	774	3000 and longer	None
" " "	15 min	Window glass	3200 and longer	None
" " "	15 min	385	3500 and longer	None
" " "	15 min	038	4300 and longer	None
Sun	20 min	None	All	None

* Hanovia Alpine Sun type, operating on a line voltage of 220 V

† Only wave lengths in the ultraviolet and visible are considered

‡ Subsequently developing into an erythematous dermatitis persisting for several days

DISCUSSION

Naturally occurring porphyrins are under suspicion as photosensitizers in man In fact, this suspicion seems to have crystallized into the belief that porphyrins are *the* sensitizers in all cases of photosensitivity, and statements to this effect are quite common We cannot find space here to discuss the origin of this idea, but only to say that the status of porphyrins as sensitizers in abnormal light sensitivity is not completely understood

It will be of interest to consider the possible relation of porphyrin to the present case Landry's syndrome is an ascending paralysis which, according to Drake (1935), may have either a toxic or an infectious background, it does not appear to be a single disease entity In a certain number of such cases porphyrin appears in the urine (see Mason et al, 1933), and there is reason to think that it would be more often found if careful search were made Although we did not demonstrate porphyrinuria in our case, there is no reason to believe that porphyrin or porphyrinogen might not have been found if more and larger urine samples had been examined Had we found porphyrin, we might have placed this case together with those of Mason, particularly since the patient was a woman, and 90 per cent of the cases of Landry's paralysis with porphyrinuria

are women (Mason et al, 1933) Porphyrin is found associated with a certain proportion of cases of *Hydroa Vacciniforme seu Aestivale* (17.5 per cent according to an analysis by Senear and Fink, 1923), which is a condition of abnormal sensitivity to light resulting in severe and often disfiguring lesions of the exposed parts. It has also been found in other cases of photosensitivity displaying other kinds of lesions (Barber, Howitt and Knott, 1926, Goekerman, Osterberg and Sheard, 1929). Furthermore, it has been demonstrated that porphyrins are photosensitizers for a wide variety of living systems (see Blum, 1932 or 1935, for an account of this type of photosensitization). Meyer-Betz (1913) produced general photosensitization in himself by the injection of a rather large dose of hematoporphyrin, and Duke (1923), Frei (1926), and Blum, Watrous and West (1935) produced local photosensitivity in human skin by the intradermal injection of this pigment. After a brief consideration of this evidence, one might seem justified in jumping to the conclusion that the sensitivity to light in the present case is the result of the presence of a porphyrin acting as a photosensitizer. In fact, this exact line of reasoning has been often followed. However, there is a very strong case against porphyrin as a sensitizer in the present instance, and we should probably find the same to be true of many others if the proper experimental evidence had been obtained. For this reason, we will consider the opposing evidence at some length.

In order for a substance to act as a photosensitizer it must absorb radiation, and it can only absorb those wave lengths which fall within its characteristic absorption spectrum. Thus the absorption spectrum of a substance should show approximately the wave length region in which it may act as a sensitizer*. While the porphyrins differ in the finer structure of their absorption in the visible region they all show a strong absorption just at the borderline between visible and ultraviolet, with a maximum at about 4000 Å. This absorption falls off to minima at about 3000 Å on the ultraviolet side, and at about 4500 Å on the visible side. Examination of the data of Hausmann and Krumpel (1927), and of Clar and Haurowitz (1933), will show the similarity of the absorption spectra of the different porphyrins in this region and that it is not greatly affected by the solvent. The spectra in the visible region vary much more for the different porphyrins, but according to the data of Clar and Haurowitz the visible absorption is very much less than that in the ultraviolet. The data of Hausmann and Krumpel would indicate a much greater absorption in the visible, but it is probable that no correction for the characteristics of their photographic plates was made in preparing their figure, so that their measurements are not quantitatively correct. Their data are nevertheless valuable in giving a comparison of the approximate positions of the absorptions of a number of different porphyrins.

The absorption spectrum of a typical porphyrin in the ultraviolet region is shown in figure 2, and it may be seen at a glance that there is no agreement between this curve and the sensitivity of our patient. In fact, our patient was sensitive in a region at which a minimum in the absorption spectrum of hematoporphyrin occurs. Furthermore, the experiments of Hausmann and Sonne (1927) and of Hausmann and Kuen (1933) on the sensitization of erythrocytes by porphyrins also demonstrate experimentally that these substances do not sensitize in the region of the normal erythemnic response, with the exception of

* A corollary of the Grotthus-Draper law, the first law of photochemistry.

mesoporphyrin, which may show some sensitizing effect in this region, but also exhibits very strong sensitization in the nearer ultraviolet and visible (Hausmann and Kuen). We have found that when the skin is sensitized locally by intradermal injection of hematoporphyrin, the response to sunlight is of the same magnitude when a filter of window glass is interposed as when exposed directly to the sun. Thus all the evidence points to the fact that the wave lengths to which porphyrins sensitize do not correspond at all with those to which our patient was sensitive.

It was suggested that the sensitization might be the result of the quinine which was given the patient some time before she entered the hospital, and to which she responded with a marked dermatitis, not, however, limited to the exposed parts as was the later dermatitis which we observed. Quinine has been stated to be a photodynamic photosensitizer by some investigators, but Frei (1926) was unable to obtain sensitization of the skin to sunlight by the intradermal injection of this drug. The absorption spectrum of quinine (Hicks, 1930, Heidt and Forbes, 1933) indicates a very considerable absorption of radiation between 3000 Å and 4000 Å, the absorption shorter than 3200 Å is considerable, but if one examines the transmittance of skin as shown in the curves of Bachem and Reed (1931) one finds that the transparency of the epidermis falls off very rapidly below 3500 Å which would tend to limit the sensitizing power of quinine in the region to which our patient demonstrated her greatest sensitivity, i.e., below 3200 Å. From a consideration of these data it appears that if quinine were the sensitizer in the present case, the patient should react to radiation much longer than that to which she is sensitive, and should be more sensitive to radiation longer than 3200 Å, than to radiation shorter than this limit. Thus, if quinine was an etiological factor in the sensitivity of the skin to light it must have acted to enhance some part of the normal photosensitive mechanism, not as a specific photosensitizing substance in the skin.

The response of normal skin to light must be rather complex. There must be first a photochemical reaction, the products of which bring about dilation of the small vessels in the skin, which is observed as erythema, and subsequently pigmentation. The steps involved may be even more numerous, and we must assume that there are a number of parts in the whole system, the hyperactivity of any one of which might result in an enhanced erythemic response. Thus it is not surprising to find that a profound and general nervous disturbance of the type occurring in our patient should be accompanied by a sensitivity to light as the normal erythemic mechanism must be affected by any disturbance in the control of the minute vessels, nor again where the administration of a drug produced marked skin changes. Such an enhanced response would, of course be produced by the same wave lengths as the normal response, and it is probable that many cases of abnormal sensitivity to light are of this type. The group of individuals ("vegetativ Stigmatisierten") whom Ellinger (1932) found to show a greater sensitivity to quartz-mercury arc radiation than normals, may probably be placed in this group. He believes this condition to be associated with thyroid gland disturbance. We see no reason, however, for believing that the thyroid gland is directly involved in the photosensitivity of our patient, but the possibility cannot be excluded. On the other hand, a number of cases have been reported in which the sensitivity lies in a wave length region outside of the normal and in which an abnormal sensitizer must be present. The cases of

Urticaria solare described by Duke (1923), Vallery-Radot et al (1926, 1928), Frei (1925), and Blum, Allington and West (1935) offer examples of the latter type, as does also the condition described by Urbach and Konrad (1929), and in all probability there are others. The position of Hydroa would seem to be questionable (see Gottron and Ellinger, 1931) and it may well be that the etiology is not the same in all the cases described under this name. Conditions involving abnormal sensitivity to light can be properly characterized only when wave length studies are carried out and it is to be hoped that these will be more frequently made in the future than in the past. We may point out that the same treatment would hardly be expected to succeed in cases of all types.

SUMMARY

1 A condition of abnormal sensitivity to light in a case of ascending paralysis, manifesting itself as an erythematous dermatitis on the face, hands and arms, is described.

2 Quartz-mercury arc radiation produced a much more severe, and persistent erythema in the skin of this patient than in normal skin, and this took on the appearance of the erythematous dermatitis displayed by the patient.

3 Only that portion of the mercury arc radiation shorter than 3200 Å was active in eliciting this erythema. The sensitivity would thus seem to be restricted to the same wave length region as the erythematous response of normal skin, and the condition could best be explained as a hypersensitivity of some part of this mechanism.

4 It is pointed out that porphyrins or quinine cannot be suspected as photosensitizers responsible for this condition.

5 The relationship to other types of photosensitivity is discussed.

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EDITORIAL

ADRENAL ATROPHY AS A CAUSE OF ADDISON'S DISEASE

Various pathologists^{1,2} have drawn attention recently to the increasing frequency with which adrenal atrophy is found as the causative lesion in Addison's disease. It was formerly estimated that atrophy was found in only about 10 per cent of the autopsies of cases of Addison's disease and tuberculosis of the adrenals in the other 90 per cent. However in recent years, as pointed out by Wells,¹ series of cases have been reported in which atrophy was found in as high as from 30 to 50 per cent of the instances.

In Brenner's review of the subject he pointed out the chief features of adrenal atrophy. It is a non-inflammatory process, including necrosis of either the adrenal cortex alone or of the cortex and medulla, followed by a disappearance of the necrotic tissue with a corresponding shrinkage of the adrenal. Ineffective regenerative changes are observed. In the type most commonly found associated with Addison's disease it is the cortical zone which has largely disappeared leaving the medulla relatively intact.

Since in the type of tuberculosis of the adrenal which is found as a cause of Addison's disease both the cortex and the medulla are usually destroyed, it might be supposed that clinical distinctions would be found to correspond with these variations in the tissue involvement accompanying these two etiologic types of Addison's disease. Wells raises the question whether longer duration and a less pronounced hypotension may not characterize the cases due to purely cortical deficiency. The matter is, however, by no means definitely settled.

The nature of the process which results in the necrosis of the adrenal cortex, with or without some medullary damage, is still quite undetermined. It is well known, however, that in experimental animals the adrenal cortex is very susceptible to bacterial toxins such as diphtheria toxin and also that human cortical tissue will show evidence of damage in all cases that have died as a result of acute infections. Basic studies establishing this fact were those of Dietrich³ during the World War. This investigator utilized the opportunities of examining healthy human glands from those who had met sudden death. With these he compared the glands removed from a series of cases in whom wound infection was the cause of death. The cortical tissue in these latter uniformly showed destructive changes.

Such cortical damage in infectious diseases is probably repaired rapidly as a rule since the cortical cells and especially those of the *zona glomerulosa* are capable of rapid regeneration. Such regeneration is readily observed in

¹ WELLS, H. GIDEON. Addison's disease with selective destruction of the suprarenal cortex, Arch Path, 1930, 1, 499-523.

² SUSMAN, WM. Atrophy of the adrenals and Addison's disease, Endocrinology, 1936, 11, 383-388.

³ DIETRICH, A. Die Nebennieren bei den Wundinfektionskrankheiten, Centralbl allg Path, 1918, 11, 169.

experimental animals. How frequently residual atrophy remains is not known.

In certain dramatic instances the damage to the adrenal in infections consists of massive hemorrhage with disintegration of the glands. These cases are marked by skin hemorrhages, vasomotor collapse and early death. The syndrome is associated especially with the onset of meningococcus infections, less frequently with those due to the pneumococcus.

No conclusive study in humans has yet shown how large a part in the clinical phenomena of acute infections may be played by less extensive forms of damage to adrenal cortical tissue. It might well be of course that such damage might result in a mingling of symptoms of acute adrenal insufficiency with those due to the other results of the infection. Moreover, besides this obvious possibility, it must be recalled that the adrenal bears some relation to bodily resistance to infection the nature of which is by no means clear. Both adrenalectomized animal and human cases of Addison's disease become abnormally susceptible to the effects of infections, and to the action of bacterial toxins and of certain poisons. Moreover it seems possible that the adrenal cortex as a storage place of cevitamic acid, which has been shown to be capable of stimulating antibody formation, plays still another rôle in connection with the bodies' response to acute infectious disease.

Susman has raised the question whether repeated past infections or poisonings may not account for the multiple atrophic spots he has noted in the adrenal cortex of some autopsy cases and suggests that possibly in susceptible individuals, more extensive damage of this kind might eventually lead to such complete cortical atrophy as would cause Addison's disease.

Another explanation of chronic cortical atrophy has appealed to Wells.⁴ He has several times drawn attention to the similarity between the pathologic cellular necrosis in cortical atrophy and that which is seen in acute yellow atrophy of the liver. Both, Wells feels, are best described as toxic cellular necrosis. Wells is inclined to carry the parallelism further and to suggest that, just as the increase of acute yellow atrophy was probably attributable to poisons such as cinchophen, so there might also be found a poison responsible for the apparent increase in the number of cases of adrenal cortical atrophy. Recently Wells encountered a case of cortical atrophy probably due to the therapeutic use of *germann* and was able to show that this drug has a fairly specific damaging effect upon the adrenal cortex of laboratory animals.

It seems apparent that this suggestion is one which clinicians should bear in mind in investigating the history of patients with Addison's disease.

M C P

⁴ WELLS, H. GIDEON, HUMPHREYS, ELEANOR M., AND WORK, EMMA G. Significance of the increased frequency of selective cortical necrosis of the adrenal as a cause of Addison's disease, Jr. Am Med Assoc, 1937, *cx*, 490-493.

REVIEWS

Bright's Disease and Arterial Hypertension By WILLARD J STONE, B Sc, M D, F A C P, Clinical Professor of Medicine, University of Southern California 352 pages, 16.5 × 24 cm W B Saunders Co, Philadelphia 1936 Price, \$5.00

This volume opens with brief historical sketches of those whose names have been associated with studies in the field of renal disease. Then follow chapters on classification of renal disease (the author presents a modification of the classification of Volhard and Fahr), renal physiology, water balance, edema, renal function tests, uremia, etc. These chapters constitute too briefly stated reviews of the more prevalently accepted current theories. There is little or no critical discussion and the author offers little in the way of personal opinion. Subsequent chapters deal with "Acute Hemorrhagic Bright's Disease, Second Stage Hemorrhagic Bright's Disease, Terminal Stage Hemorrhagic Bright's Disease, Acute and Chronic Degenerative Bright's Disease." Forty-four pages are devoted to arterial hypertension, arteriosclerosis and arteriosclerotic Bright's disease. This latter subject is divided into latent and active forms by the author. The second part of the title seems scarcely justified by the amount of discussion given it as such. The 140 autopsied cases of Bright's disease are abstracted too briefly to be very instructive.

W S L, JR

Dextrose Therapy in Everyday Practice By E MARTIN, Sc D 451 pages, 16 × 24 cm Paul B Hoeber, Inc, New York 1937 Price, \$3.00

An impersonal digest of significant dextrose literature since 1900, this readable book correlates experimental laboratory and clinical findings with admirable brevity. More than a handbook, it succeeds in giving a dextrose-eye view of metabolism without losing yardage in controversy or flight of fancy. The first portions dealing with chemistry and physiology show occasional proof-reader's errors (*normal blood sugar range is from 0.8 to 0.12*) which tend to shake faith in figures quoted which are less familiar. The author is strict enough too in insisting on the substitution of chemically correct *dextrose* for the familiar *glucose* of common parlance. Yet later on he uses *glycolysis* where *glycogenolysis* is apparently meant. The latter portions of the book show the difficulty of the pure-scientist-in-medicine's uncritical acceptance of medical literature at its face value (as where on p. 110 he so glibly speaks of *simple blockage of the reticuloendothelial system*). His therapy has a Gould and Pyle-ishness throughout that is most dangerous in the genito-urinary section where he is still in the intravenous mercurochrome era. The charts are good, and the pictures better than average. Definitely a transition book, it would interest the clinically-minded second-year, and the chemically-minded third-year medical student, and be helpful provided that the student remembers that dextrose is but one of many therapeutic agents.

C A

Gastrosocopy The Endoscopic Study of Gastric Pathology By RUDOLF SCHINDLER, M D 343 pages, 17.5 × 25 cm University of Chicago Press, Chicago, Ill 1937 Price, \$7.50

Every chapter in the book is full of valuable information. The technic of gastrosocopy is clearly and concisely stated. The splendid description of the procedure will be extremely helpful to those who desire to do gastrosocopy. To those not desir-

ing to do gastroscopy, it will materially broaden their knowledge of the technical side of the procedure. When technical problems do occur, they are comparatively easy to overcome if one follows the directions as outlined in the chapter on technic. The reviewer has followed very closely the technic as outlined, and has found it most satisfactory. The position of the patient for emptying the stomach is of the utmost importance, and this has been stressed by the author. Likewise, the orientation of the instrument in the stomach has been described thoroughly. This, of course, is very necessary, so as to be able at all times to know which portion of the stomach is being observed.

Many diagrams have been used to show the portion of the stomach visualized, with the instrument at different levels, and when the instrument is rotated in different positions. Great detail concerning orientation is of the utmost importance. The technic of introducing the gastroscope can be mastered in a very short time, but to be able to determine accurately the portion of the stomach under observation, requires a great deal of training. The gastroscopic appearance of the normal stomach is extremely well presented. After all, one must be perfectly familiar with the picture of the normal stomach before attempting to study gastric pathology.

In the study of gastric pathology, the author stresses two important diagnostic procedures, namely roentgen-ray relief studies, and gastroscopy. Both have a definite place in the diagnosis of gastric lesions. The two methods bear a supplementary relation to each other. Certain facts may be obtained by one procedure, and other very definite facts obtained by the other.

The author definitely favors gastroscopy in studying the different types of gastritis. His classification of the different types of gastritis is all that can be desired, the different types are easily recognized gastroscopically. In the diagnosis and treatment of gastric ulcer, the author stresses the importance of gastroscopy, and urges the advantage of frequent gastroscopic examinations to determine what results are being obtained from treatment. In the diagnosis of carcinoma, he believes a positive diagnosis can be made by roentgen-ray relief studies and gastroscopy. He does not believe there is any necessity for surgical exploration of the abdomen in any case in order to make the diagnosis. He makes a strong plea for roentgen-ray relief study and thorough gastroscopic examination, and states that the two methods of examination will give one the correct diagnosis in almost every case. The reviewer believes that in order to make the diagnosis of carcinoma by these two methods alone, one must have had a vast amount of experience in gastroscopy, and in the interpretation of roentgen-ray relief studies. In determining the etiology of obscure gastric hemorrhage, the great advantages of gastroscopy have been thoroughly discussed.

In addition to the clear and concise manner in which gastroscopy has been discussed, the book contains a very complete bibliography of the subject, and 96 perfectly splendid color plates. One not familiar with gastroscopy might be inclined to doubt the brilliant colors found in the plates. The reviewer, however, from his own experience, believes that the colors are not exaggerated, but quite clearly represent different phases of gastric pathology. With each color plate, there is a short discussion of what it represents.

The book should be of real value to every internist, and especially to those limiting their practice to gastroenterology. It is of course, of the utmost value to those interested in gastroscopy. The reviewer is of the opinion that gastroscopy as a diagnostic procedure is just as valuable as the roentgen-ray, in the diagnosis of gastric pathology. It in no way replaces roentgen-ray studies—they both bear a supplementary relation to each other.

E B F

Endocrinology Clinical Application and Treatment By AUGUST A. WERNER, M.D., F.A.C.P. 672 pages, 15 × 24 cm Lea and Febiger, Philadelphia 1937 Price, \$8.50

Quite a number of texts on endocrinology have been published within the past few years. On greeting a new publication one is interested to see how it differs from, or what it adds to, those already available.

This particular work contains many valuable data amassed from the author's large practice and wide experience. There are many case reports and many illustrations. The classical endocrine syndromes are well delineated.

In the opinion of the reviewer, the book is marred somewhat by the enthusiastic inclusion of many conditions of unknown origin as of probable or possible endocrine etiology.

The illustrations in general are excellent but there are included some of questionable choice, notably that illustrating lipodystrophia progressiva, a very good photograph of a very fat woman but lacking the essential characteristic of this rare anomaly, namely, the remarkably complete emaciation above the waist.

The book gives a good idea of the methods of practice of an enthusiastic and well informed endocrinologist.

T P S

The Digestive Tract A Radiological Study of Its Anatomy, Physiology and Pathology By ALFRED E. BARCLAY 427 pages, 19 × 25 cm Cambridge University Press Department, Macmillan Co., New York 1937 Price, \$12.00

A striking feature of this book is that the author obviously considers an understanding of the normal, an essential prerequisite to the evaluation of pathological change, since he devotes roughly the first half of his book to anatomy and physiology from the point of view of the radiologist. Included in this discussion are summaries of some of the latest researches on the digestive tract.

The book is divided into three main parts. Part I is devoted to technic including not only a careful review of routine measures employed in the practice of radiology but also stressing some of the dangers associated with this work. The completeness and the clarity of Part I set a high standard.

In Part II, devoted to the radiological examination of the "normal" gastrointestinal tract, the first section includes a discussion of the anatomy of the "normal" stomach and the inherent mobility and adaptability of the abdominal viscera. In this section the alimentary tract is considered as a whole and the justifiable conclusion is reached that an alimentary tract may approximate the average, but that there is no fixed standard of normality. The factors influencing the form and position of the stomach, the effects of posture and respiration and the mobility and adaptability of the viscera are discussed in detail.

Section II of Part I, devoted to physiology, reviews the movement of food from mouth to anus as observed by the radiologist. The process of swallowing, gastric peristalsis, pyloric sphincter activity as well as the intestinal movements, are all portrayed radiographically. The author's discussions are thought-provoking as can be seen from his statement that gravity and tonic action appear to play a part in the control of the pyloric sphincter but that the peristaltic waves seem to be identical whether the sphincter relaxes or not. Moreover, he is certain that the opening of the pylorus does not depend on the acidity or alkalinity of the food.

On the basis of this thorough presentation of anatomy and physiology the author develops Part III which is devoted to pathology. From the esophagus and through the colon, in logical sequence, the reader has presented to him a fascinating discussion of "roentgenologic pathology." An excellent chapter on the gall-bladder is included.

The author never attempts to be dogmatic and often admits the inadequacies of roentgenologic diagnosis, as, for example, in his discussion of gastritis

The last quarter of the book presents seven appendices which must be invaluable to the roentgenologist and especially to the beginner in this specialty. The bibliography is apparently up to date and the division of indices into both an author and a general index, is always a convenience to the reader.

The book represents a well written, well illustrated text which could only be the outcome of an unusual roentgenologic experience.

S. M.

COLLEGE NEWS NOTES

GIFTS TO THE COLLEGE LIBRARY

Grateful acknowledgment is made of the receipt of the following donations to the College Library of publications by members

Books

- Dr H A Pattison (Fellow), Livingston, N Y, ' Potts Memorial Hospital A Review of Activities of the First Ten Years with a Report of a Special Survey Committee ',
Dr Edward Weiss (Fellow), Philadelphia Pa " Practical Talks on Kidney Disease "
Dr John Zahorsky (Fellow), St Louis, Mo " Baby Incubators," " Golden Rules of Pediatrics," " Pediatric Nursing " and " Synopsis of Pediatrics "

Reprints

- Dr E J G Beardsley (Fellow), Philadelphia Pa —1 reprint,
Dr Victor W Bergstrom (Fellow), Binghamton, N Y —1 reprint,
Dr George Blumer (Fellow), New Haven Conn —6 reprints,
Dr Coursen B Conklin (Fellow), Washington, D C —3 reprints,
Dr Edward E Cornwall (Fellow), Brooklyn, N Y —8 reprints,
Dr Norbert Enzer (Fellow), Milwaukee Wis —1 reprint,
Major C J Gentzkow (Fellow), M C, U S A —1 reprint,
Dr George T Harding, III (Fellow) Columbus, Ohio —1 reprint
Dr Arthur A Herold (Fellow), Shreveport, La —1 reprint,
Lt Col Charles C Hillman (Fellow), M C, U S A —3 reprints,
Dr Charles E Homan, Jr (Fellow), Hartford, Conn —1 reprint,
Dr Philip B Matz (Fellow), Washington, D C —1 reprint,
Dr Warren W Quillian (Fellow), Miami, Fla —3 reprints,
Dr R J Reitzel (Fellow), San Francisco, Calif —1 reprint,
Dr F L Roberts (Fellow), Trenton, Tenn —1 reprint,
Dr Edward Schons (Fellow), St Paul Minn —1 reprint,
Dr Philipp Schonwald (Fellow), Seattle, Wash —1 reprint,
Dr W Warner Watkins (Fellow), Phoenix, Ariz —2 reprints,
Dr Clarence R Bennett (Associate), Eufaula, Ala —1 reprint,
Dr John Francis Briggs (Associate), St Paul, Minn —7 reprints,
Dr Hyman I Goldstein (Associate), Camden, N J —1 reprint
Dr William H Gordon (Associate), Boston, Mass —2 reprints,
Dr W H Griffith (Associate), Huron, S D —1 reprint
Dr Charles Solomon (Associate), Brooklyn, N Y —2 reprints

Dr Roy R Kracke (Fellow) Emory University, Ga, has been elected a member of the American Board of Pathology for a term of six years Dr Kracke is also chairman of the Section on Pathology and Physiology of the American Medical Association

Dr William E Robertson (Fellow), Philadelphia, is now President of the Philadelphia County Medical Society Dr Louis H Clerf (Fellow), Dr Michael A Burns (Fellow) and Dr Isidore Kaufman (Fellow) are directors

Dr E J G Beardsley (Fellow), Philadelphia, is Secretary-Treasurer of the American Association of the History of Medicine

Dr William D Stroud (Fellow), Philadelphia, is President of the Philadelphia Heart Association, Dr David Riesman (Fellow), Vice President Dr Thomas M McMillan (Fellow), Secretary, Dr Edward E Krumbhaar (Fellow), a member of its board of governors

Dr Ross McClure Chapman (Fellow), Towson, Md, is President of the American Psychiatric Association, Dr J Allen Jackson (Fellow), Danville, Pa, and Dr Walter L Treadway (Fellow), U S Public Health Service, are members of the executive committee

Dr Edward S Sledge (Fellow), Mobile, Ala, is President of the Alabama State Medical Association

Dr Paul A Yoder (Fellow), Winston-Salem, N C, is President of the Eighth District Medical Society of that State

Dr John W Tappan (Fellow), El Paso, Tex, has been made Health Officer of the El Paso City and County Health Unit

Dr Dudley C Smith (Fellow) is President of the University of Virginia Medical Society

Dr Charles W Waddell (Fellow), Fairmont, W Va, is President of West Virginia State Medical Association, Dr A A Shawkey (Fellow) Charleston, is Second Vice President and Dr T M Barber (Associate), Charleston, is Treasurer

The Fifth International Congress of Radiology was held in Chicago, September 13 to 17, with a large delegation from Europe, Mexico, Canada and South America. This was the first time the Congress has met in the United States. Dr B H Orndoff (Fellow), Chicago, was Secretary of the Congress, Dr Arthur C Christie (Fellow), Washington, was chairman of the Executive Committee, Dr George E Pfahler (Fellow), Philadelphia, was an honorary vice president

Dr E H Shuller (Associate), McAlester, Okla, is President of the Southeastern Oklahoma Medical Association

Dr J A Myers (Fellow), Chief of the Chest Clinic at the University of Minnesota and President of the National Tuberculosis Association, will be the guest speaker at the Post-Graduate Course on Tuberculosis to be conducted in Oklahoma City, October 13

Dr Clarence H Webb (Fellow), Shreveport, La, is President of the Louisiana State Pediatric Society

Dr Horace W Soper (Fellow), Dr Frank D Gorham (Fellow) and Dr Lee Pettit Gay (Fellow), all of St Louis, are President, Vice President and Treasurer, respectively, of the Missouri Society for the Advancement of Gastro-enterology

Dr Henry K Speed (Fellow), Sayre, Okla., is President-Elect of the Oklahoma State Medical Association

Dr O B Kiel (Fellow), Wichita Falls, Tex., is President of the Texas State Board of Medical Examiners

Dr Edward H Schwab (Fellow), Galveston, Dr M D Levy (Fellow), Houston, and Dr Robert M Barton (Fellow), Dallas, are President, Vice President and Secretary-Treasurer, respectively, of the Texas State Heart Association

Dr Bedford Shelmire (Fellow), Dallas, is President of the Texas Dermatological Association

Dr John G Young (Fellow), Dallas, is President of the Texas Pediatric Society

Dr John A McIntosh (Fellow), San Antonio, is Second Vice President of the Texas Neurological Association

Dr May Owen (Fellow), Fort Worth, Tex., recently received the honorary degree of Doctor of Science, conferred by the Texas Christian University

Dr Edward J Van Liere (Fellow), Morgantown, has been appointed Dean of the West Virginia University School of Medicine

Dr Ernest D Hitchcock (Fellow), Great Falls, is Vice President of the Montana State Medical Association

Dr David Riesman (Fellow), Philadelphia, emeritus professor of clinical medicine and professor of the history of medicine, University of Pennsylvania School of Medicine, was recently the recipient of the honorary degree of Doctor of Laws, conferred by the University of Wisconsin

Dr Jacob C Geiger (Fellow), Director of Public Health for the City and County of San Francisco, was recently elected President of the Pasteur Society of Central California

Dr Russell H Oppenheimer (Fellow), Dean of Emory University School of Medicine and heretofore Superintendent of Emory University Hospital, Atlanta, has been made Medical Director of the Hospital

Dr Hugo A Freund (Fellow) was recently appointed a member of the Public Welfare Commission of Detroit

Dr James J McGuire (Fellow), Trenton, is Secretary of the New Jersey State Board of Medical Examiners

Dr William de B MacNider (Fellow), Chapel Hill, Kenan Research Professor of Pharmacology at the University of North Carolina School of Medicine has recently been appointed Dean, to succeed Dr Charles S Mangum

Dr Robert Finley Gayle, Jr (Fellow), Richmond, is one of the physicians ap-

pointed to a new board created to have supervision over state mental hospitals in Virginia

Dr Charles E Sears (Fellow), Portland, Ore, was elected President of the Pacific Northwest Medical Association during July

Dr T Grier Miller (Fellow), Philadelphia, Professor of Clinical Medicine in the University of Pennsylvania School of Medicine and Chief of the Gastro-Intestinal Section, Hospital of the University of Pennsylvania, will have charge of the newly established "Kinsey-Thomas Foundation for the Study and Treatment of Diseases of the Digestive System" at the University of Pennsylvania. The late Miss Frances T Kinsey provided \$200,000 in her will for the establishment of the Foundation

The estate of the late Dr James M Anders (Master), Philadelphia, amounting to over \$500,000, has been ordered distributed. Dr Anders' will provided bequests of \$2,000 to the Philadelphia County Medical Society Library Fund and \$1,000 to the Society's Aid Association. It also provided \$2,500 for the Board of Directors of the Philadelphia County Medical Society to be held in trust and to be used to meet the expenses of the Philadelphia celebration of the Annual Health Day, a project in which Dr Anders was deeply interested and which he founded. The residuary estate was left in trust, the income to go to Mrs Anders for life. When the trust is ended, \$50,000 is to go to the trustees of the University of Pennsylvania for the Endowment Fund of the Graduate School of Medicine of the University

Dr Thomas B Magath (Fellow), Rochester, Minn, has been chosen President-elect of the American Society of Clinical Pathologists

Under the presidency of Dr J Morrison Hutcheson (Fellow and Governor), Richmond, the Medical Society of Virginia will hold its annual meeting in Roanoke, October 12 to 14. Among the invited guests are Dr Russell L Cecil (Fellow), New York City, and Surgeon General Thomas Parran (Fellow and Governor), of the U S Public Health Service

Dr George B Lawson (Fellow), Roanoke, was recently reappointed by the Governor as a member of the State Board of Health, his term of office to continue until 1942

Dr Louise Taylor Jones (Fellow), McLean, Va, one of the Vice Presidents of the Medical Women's International Association, attended the Fourth Congress held in Edinburgh, Scotland, July 13 to 18

Dr Elizabeth Bass (Fellow), New Orleans, La, attended the Medical Women's International Association in Edinburgh, Scotland, July 13 to 18, as a councillor from the American Medical Women's Association

The degree of Doctor of Laws was conferred upon Dr C C Bass (Fellow), Dean of Tulane University School of Medicine by Duke University at the annual commencement, June 7

The Southern Tuberculosis Conference will hold its annual meeting at the John Marshall Hotel, Richmond, Virginia, September 29, 30 and October 1, 1937. Among the speakers will be Paul H Ringer, M D (Fellow), Asheville, North Carolina, J A Myers, M D (Fellow), University of Minnesota, Louis Hamman, M D (Fellow), Johns Hopkins School of Medicine, Horton Casparis, M D (Fellow), Vanderbilt University School of Medicine, L J Moorman, M D (Fellow), Oklahoma City

OBITUARIES

DR JOSEPH LEGGETT MILLER

Dr Joseph Leggett Miller (Fellow), Chicago, Ill., died near Great Falls, Montana, on August 6. Death was sudden. He had gone to Montana on his annual vacation. Dr Miller was a native of Kewanee, Illinois, where he was born November 24, 1867. He received his Bachelor's degree from the University of Michigan in 1893. Two years later he graduated in Medicine at Northwestern University Medical School. He served his internship at Mercy Hospital in Chicago, and then became associated with Dr Frank Billings.

Dr Miller became a teacher at Rush Medical College in the Department of Medicine, eventually becoming Professor of Medicine. Since 1924 he was Clinical Professor of Medicine at the University of Chicago. For years he was a member of the Attending Staff at the Cook County Hospital. For some time he served as president of the Staff. For many years he was Attending Physician at St. Luke's Hospital.

He was a member of the American Medical Association, having served as secretary of the section on Practice of Medicine for five years, and as chairman of the same section in 1908-1909. He was a member of the Association of American Physicians, the American Society for Clinical Investigation and the Central Society for Clinical Research. He was a member of the Chicago Society of Internal Medicine, which he once served as president. Likewise he was a member and past president of the Chicago Institute of Medicine. He was also a member of the Chicago Medical Society and the Illinois Medical Society. He had been a member of the American College of Physicians since 1929.

He served in the World War, first as Major and later as Lieutenant Colonel in the Medical Corps. For many months he was chief of the Medical Department at Camp Dodge. From 1909 until 1931 he was Editor-in-Chief of the Archives of Internal Medicine. He also contributed largely to medical literature. Dr Miller had a wide reputation as a teacher and investigator and a contributor to the literature. He had a great gift for friendship, he was widely known, admired and beloved, unassuming and frank in conversation, exceptionally clear and direct in his teaching, a genial companion and loyal friend, and a physician who exemplified the old virtues of which the profession is so proud.

JAMES G. CARR, M.D., F.A.C.P.,
Governor for Northern Illinois

DR JUDSON DALAND

The death of Dr Judson Daland (Fellow) of Philadelphia on August 14, 1937, at 77 years of age removes a well known distinguished and

picturesque personality from the medical profession and from the citizenry of his adopted city and state

Dr Daland had been in ill health for two years, as the result of an automobile accident in England and from a subsequent major operation, and his passing was a happy release from increasing infirmities. Born in New York, in 1860, Judson Daland attended the medical school of the University of Pennsylvania and graduated in 1882. Shortly after his graduation he established his practice in Philadelphia and began forming the professional associations of a long and active life.

He was, from his earliest years, deeply interested in all aspects of science, especially biological science, and soon became interested in teaching and, early, affiliated with the Medico-Chirurgical Medical School and Hospital. Revealing his ability, talent and worth as a medical practitioner, investigator, teacher and writer Dr Daland was advanced in teaching positions until he became, in 1903, the Professor of Clinical Medicine in the Medical School and Attending Physician to its Hospital. Judson Daland's greatest contribution to clinical medicine was in emphasizing and reemphasizing the direct relationship of focal infections in the teeth, tonsils and sinuses to local (and frequently misunderstood) symptoms and to the general health conditions of patients at a period in medical history when such a relationship was denied, ignored and, all too often, derided by the majority of the, so termed, leaders of the medical profession. Dr Daland was, from his earliest years in medicine, deeply interested in tropical diseases and pursued knowledge in this subject in many lands. He was one of the earliest observers to point out that tropical diseases were to be found remote from the tropics and he had many opportunities of illustrating the truth of his statement by demonstrating patients in his Philadelphia clinic that were suffering from such maladies as pellagra, sprue, yaws, filariasis, beri-beri, quartan malaria and leprosy. In no Philadelphia clinic of that period was as much attention given to the seldom encountered disorders as was true in Dr Daland's service and the reason for this is to be found in Dr Daland's frequent visits to the tropical countries and his entire familiarity with the diseases of those sections.

During Dr Daland's active professional life he was a much sought consultant and served in such a capacity in a number of the city's and state's hospitals.

When the Medico-Chirurgical Medical School merged with the Medical School of the University of Pennsylvania to become the Graduate School of that great institution Dr Daland became a Professor of Clinical Medicine in the Graduate School and continued this association until his retirement from practice when he became Emeritus Professor of Clinical Medicine.

Dr Daland was an exceptional man in the medical profession for, in addition to being a nationally and internationally recognized expert in medical science, he was, perhaps, even better known as a world traveller.

an archeologist, a paleontologist, a connoisseur of art, a musician of ability, an accomplished linguist and a sportsman well known in many of the obscure corners of the world. In recent years Dr Daland has devoted much time and thought to the activities of the Philadelphia Institute for Medical Science, now active within the walls of the Philadelphia General Hospital, of which organization he was one of the founders and its first president and to which, it is said, he has bequeathed his \$200,000 estate.

Dr Daland represented an unusual type of a rapidly passing generation. Is it not possible that his life, his experiences, his education, that continued to the very end of his life, hold a lesson for the members of a younger generation?

Here was a physician who possessed an exceptional education in medicine and in life. He was cultured, travelled and truly learned but the more he knew the more modest he became concerning his many accomplishments and the more conscious he was of his ignorance concerning many of life's secrets. It is said that he wished his ashes to be placed in an urn in the Philadelphia Philosophical Society's rooms where he had spent so many pleasant hours and that upon the urn he wished placed the words, "I sought Truth."

Could any physician desire a better epitaph?

E J G BEARDSLEY, M D , F A C P ,
Governor for Eastern Pennsylvania

DR ELMER L EGGLESTON

Dr Elmer L Eggleston (Fellow), Battle Creek, Mich., died after three days' illness, July 7, 1937, of coronary thrombosis.

He was born in Marion, Iowa, in 1874. He received his M D degree from American Medical Missionary College (Chicago), 1900. He did post-graduate work at the New York Post-Graduate Medical School in Vienna. At the time of his death, he was head of the Department of Internal Medicine, Group B, Battle Creek Sanitarium. He was the author of several published articles, usually pertaining to gastroenterology. Dr Eggleston was a member of the Northern Tri-State Medical Society, Mississippi Valley Medical Society, Calhoun County Medical Society, Michigan State Medical Association, and a Fellow of the American Medical Association. He was elected a Fellow of the American College of Physicians on April 6, 1922.

His medical career was entirely devoted to institutional work at the Battle Creek Sanitarium, having taken his internship there and followed as assistant physician and finally head of the above mentioned department. For approximately 20 years he devoted himself largely to the subject of gastroenterology. Dr Eggleston possessed an unusual personality and with it went a keen mind and a sympathetic character, which fitted him so admirably for his medical career. During his years of work he met a great many prominent people from all parts of the United States, all of whom

became his devoted friends. They all appreciated his sympathetic personal devotion to them. He had an aptness for recognizing not only their physical ills, but also was able to help them adjust themselves to any complexes they might have established as a result of anxiety, worry and trouble. Each year he witnessed the return of old patients and many patients referred by Doctors and friends, which proved above everything else his success as a physician. He had many local friends and patients who leaned heavily on him and his death was a shock to not only these, his friends and neighbors, but to former patients in all parts of the county. Scores of telegrams and floral tributes further proved the love and esteem of those that knew him.

A paragraph from an editorial portrays Dr. Eggleston as he was known at home. "The professional loss through Dr. Eggleston's passing will be widely recognized. But Battle Creek, to which he belonged and into which he built the strong attachments of Home, grieves for the loss of a friend and fellow citizen who made himself endeared here because, in so many ways of helpful service, he had practiced that philosophy which he gave to the troubled patients—and had made the most of his todays."

M. A. MORTENSEN, M.D., F.A.C.P.

DR. JACOB FOWLER AVERY

Dr. Jacob F. Avery, a Fellow of the College, died at La Jolla, California, June 25, 1937. Dr. Avery had been retired from active practice for the past four years due to coronary disease, which resulted in his death.

Dr. Avery was born at Poughkeepsie, New York, January 19, 1873. He was graduated from Minneapolis Central High School in 1892 and from the University of Minnesota, College of Medicine, class of 1899. Following his internship at the City Hospital (now Minneapolis General Hospital), Dr. Avery practised in Virginia and Aitken, Minnesota before locating in Minneapolis in 1906. He retired from active practice in April 1932.

Dr. Avery was elected to membership in the Hennepin County Medical Society December 3, 1906. He became an Emeritus member in 1933 and an affiliate member of the Minnesota State Medical Association the same year.

He was married to Mary L. Esmond, June 4, 1902, who, with one son, Esmond Avery, of Detroit, Michigan, survives him.

Dr. Avery was commissioned a Captain in the Medical Corps, U. S. Army, July 10, 1917, and served with the 44th Infantry and the 39th Field Artillery at Camp Lewis, Washington. He was discharged at Camp Dodge, Iowa, October 14, 1919. For two years he served as chief of Medical Hospital Service in Minneapolis (this was forerunner of the Veterans' Administration).

He was a Fellow of the American College of Physicians and, until his

retirement, a member of the Minnesota Society of Internal Medicine In Minneapolis he was a member of the staffs of Northwestern Hospital and Abbott Hospital

JAMES F CHURCHILL, M D , F A C P ,
Governor for Southern California

DR FRANK ALSWORTH WAPLES

Dr Frank Alsworth Waples (Fellow), Houston, Texas, died March 3, 1937 He was born in New Orleans, Louisiana, in 1868 He held the degrees of Bachelor of Science and Doctor of Medicine from the University of Michigan From 1894-98, he was in charge of a general hospital in Kolgan, China From 1905-10, he conducted a private hospital in Cody, Wyo He was later on the staff of the Clifton Springs Sanatorium, of Clifton Springs, N Y, and Phelps Sanatorium, Battle Creek, Mich He later joined the staff of the Southern Pacific Hospital at Houston, Texas, and was internist to the Southern Pacific Lines

Dr Waples was a member of the Harris County Society, Texas State Medical Association, American Medical Association, and had been a Fellow of the American College of Physicians since 1920

DR AUGUSTUS WARREN CRANE

Dr Augustus Warren Crane (Fellow), Kalamazoo, Michigan, died February 20, 1937, of coronary thrombosis Dr Crane was born in Adrian, Mich, in 1868 He received his medical training at the University of Michigan Medical School, graduating in 1894 He was a member and past-president of the American Roentgen-Ray Society, a member of the Radiological Society of North America, a member of the American College of Radiology, an honorary member of the London Roentgen-Ray Society, a member and past-president of the Kalamazoo Academy of Medicine and Michigan Association of Radiologists In 1921 he was awarded the gold medal by the Radiological Society of North America He was a former acting editor and later a member of the editorial board of the *American Journal of Roentgenology* Kalamazoo College and the University of Michigan both honored him by conferring honorary degrees upon him He was chairman of the Kalamazoo County Section of the Michigan State Committee of Medical Preparedness, and was a member of Michigan Medical Advisory Board during the World War

DR JAMIE W DICKIE

Dr Jamie W Dickie of Southern Pines, N C, was born near Henderson, N C, October 25, 1893, the son of George T and Manolia Coppedge Dickie He graduated from Wake Forest College in 1914, receiving his

doctor's degree from Jefferson Medical College in 1917, and immediately joined the U S Navy Medical Corps, and was stationed at Fort Lyons, Colorado. He received his discharge in 1919, and for two years became associated with the late Dr W L Dunn of Asheville, specializing in pulmonary diseases.

He then went to Southern Pines, N C , where he established Pine Crest Manor Sanatorium, which has been in successful, continuous operation since. This institution is devoted to the study and treatment of pulmonary diseases.

Dr Dickie did postgraduate work on many occasions, having spent the entire past winter at the University of Pennsylvania and at Peter Bent Brigham Hospital in Boston. He had only returned to his work a few days when he was taken with pneumonia from which he died July 6, 1937.

His publications were not numerous, and were on subjects related to the chest. As an avocation, however, he wrote short stories and poems, and was widely interested in literature, particularly biography.

He was a member of his County and State Medical Societies, a Fellow of the American Medical Association, and became a Fellow of the American College of Physicians in 1936. He was a director of the North Carolina Tuberculosis Association and a member of the National Tuberculosis Association.

He was a member of the Episcopal Church. He leaves in addition to his wife, who was Miss Inez Benthall, a son, David Henry, and one daughter, Jane.

Dr Dickie was a man of great personal charm, of good judgment and wide knowledge in his chosen sphere of medical activities, and his sudden passing at an all too early age will leave a gap in the medical profession of this section that will be hard to fill.

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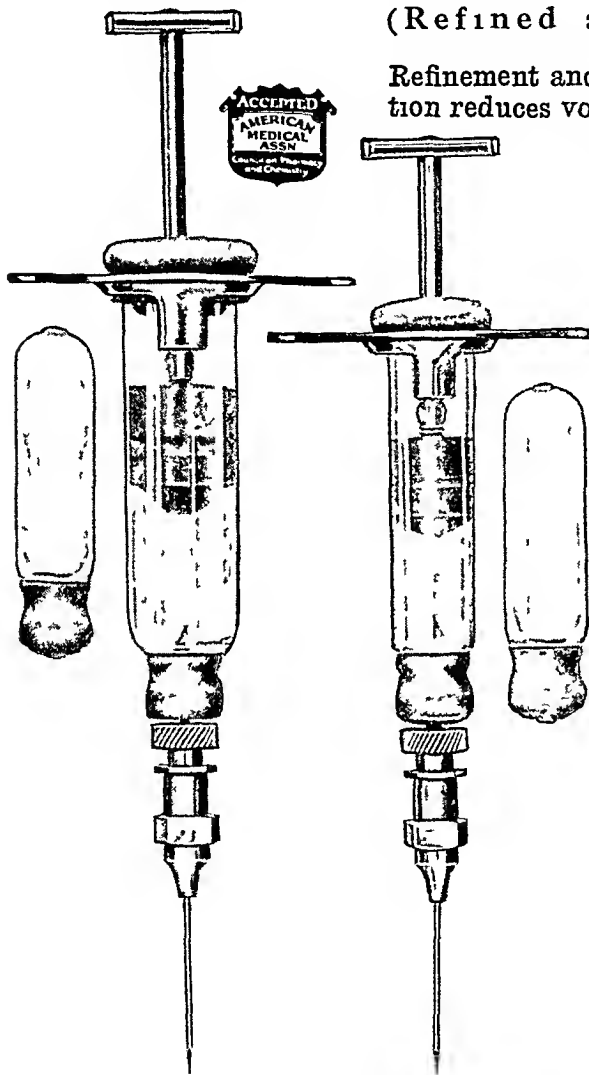


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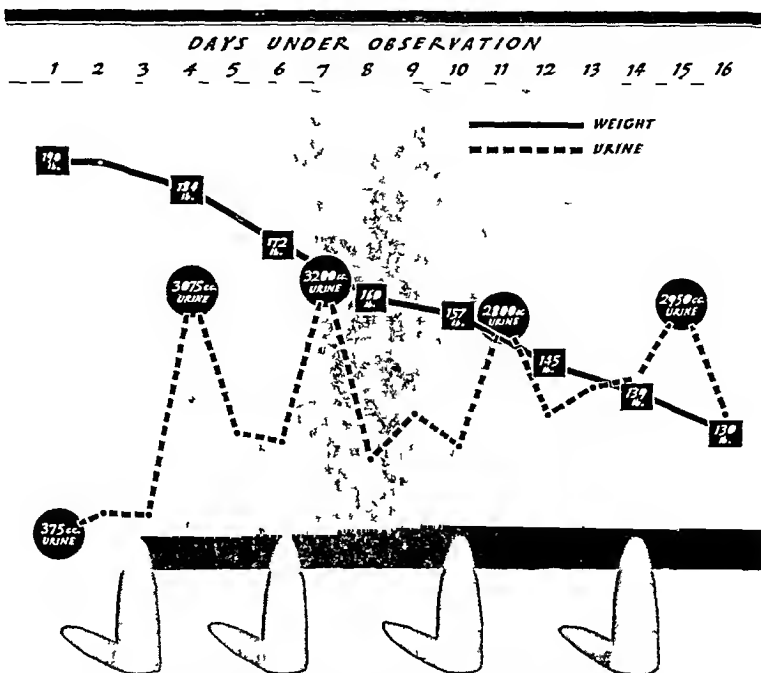
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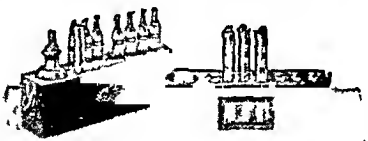
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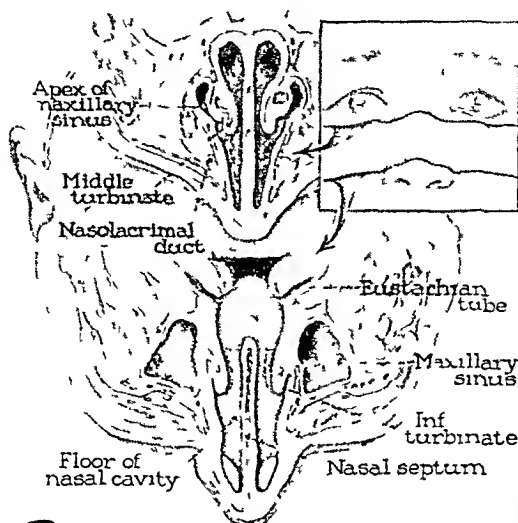
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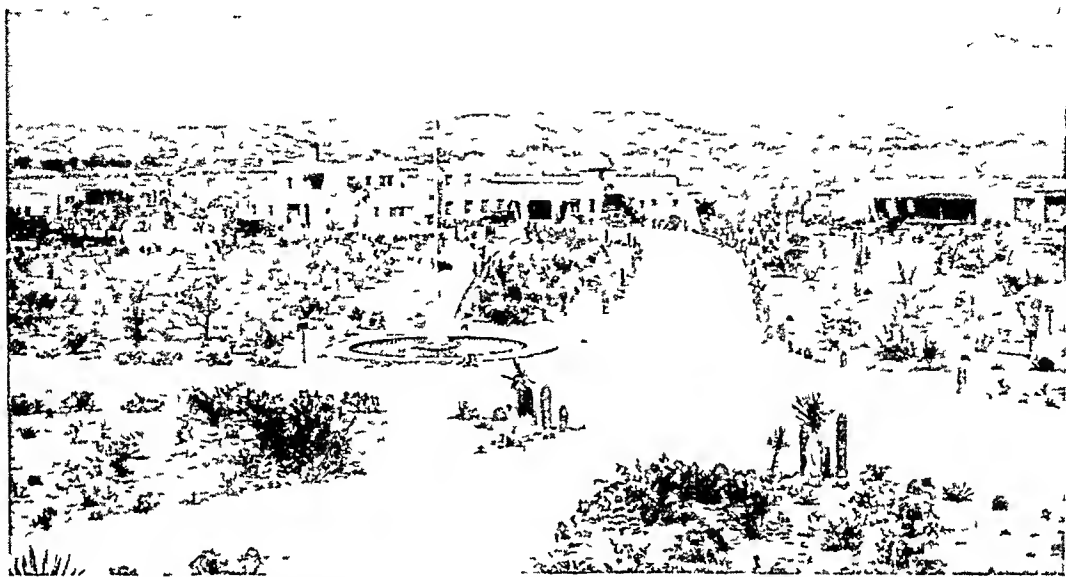


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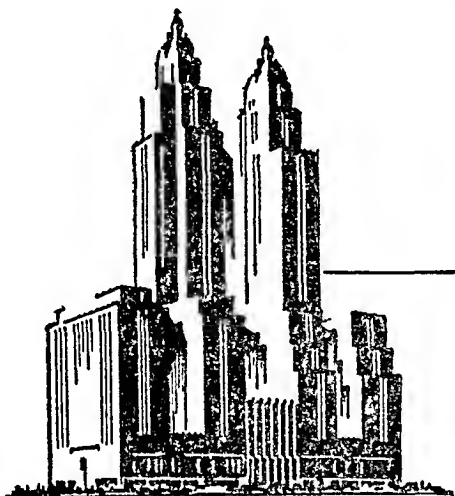
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Place of Publication—Prince and Lemon Sts, Lancaster, Pa

Editorial Office—University Hospital,
Baltimore, Md

Executive Office—4200 Pine Street,
Philadelphia, Pa

THE ANNALS OF INTERNAL MEDICINE is published by the American College of Physicians. The contents consist of contributions in the field of internal medicine, editorials, book reviews, and a section devoted to the affairs of the College.

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ANNALS OF INTERNAL MEDICINE

PUBLISHED BY

The American College of Physicians

VOL 11 (OS, Vol XVI)

OCTOBER, 1937

NUMBER 4

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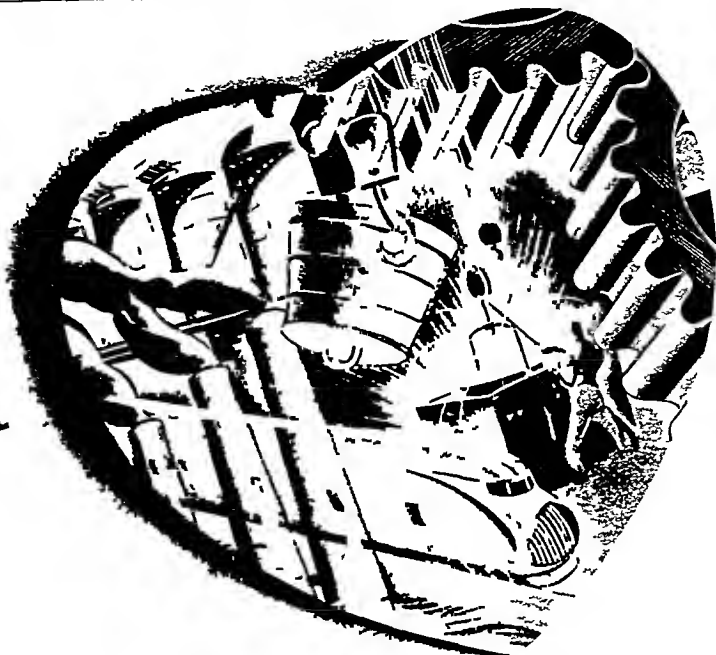


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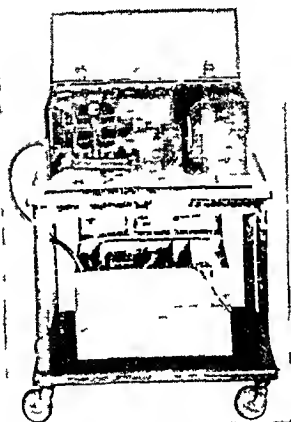
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FIG 2 11 50 A M Maximum shrinkage evident



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¹ Cole, Harold N, *et al*, J A M A 108 22, 1937

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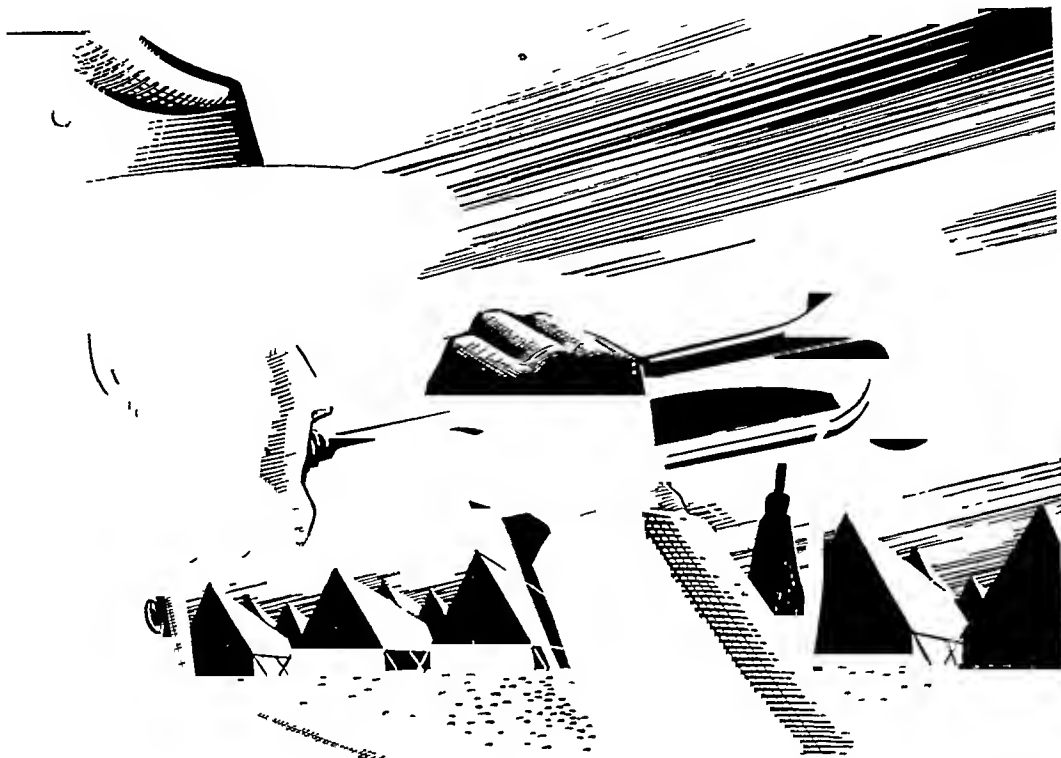
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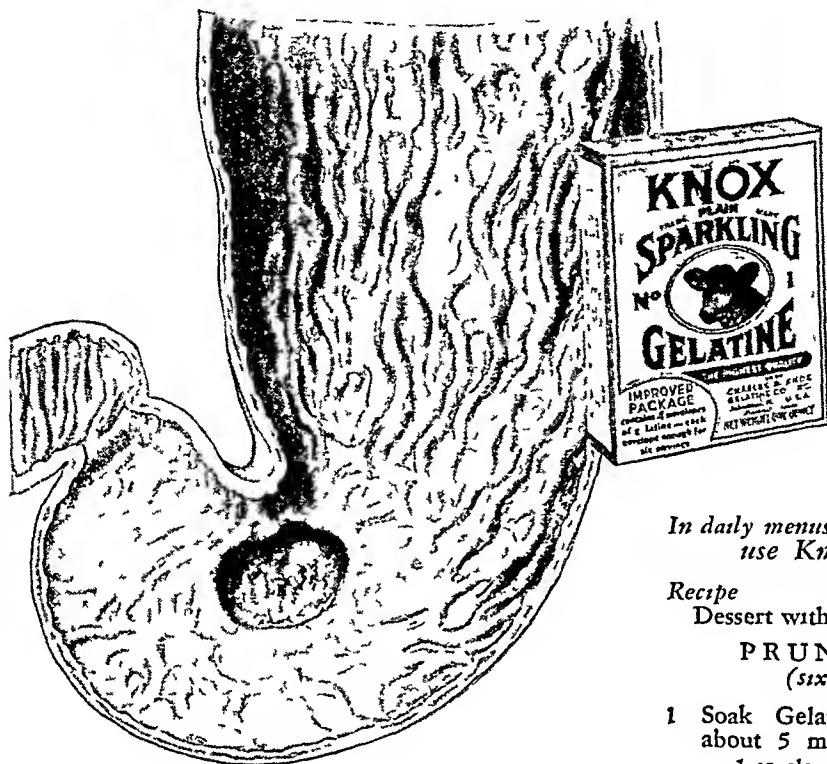
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 - $\frac{1}{2}$ cup sugar
 - $\frac{1}{4}$ teaspoonful salt
- 3 Cool. When mixture begins to thicken, fold in
 - 2 egg whites, stiffly beaten
- 4 Rinse mold or dish in cold water, and fill with dessert. Chill. To serve, unmold and garnish with whipped cream, or serve with custard sauce.

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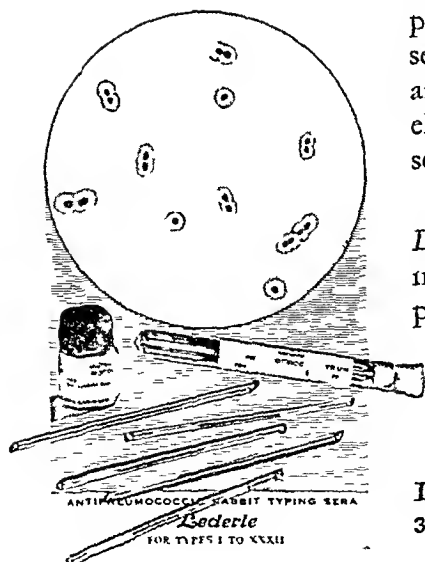
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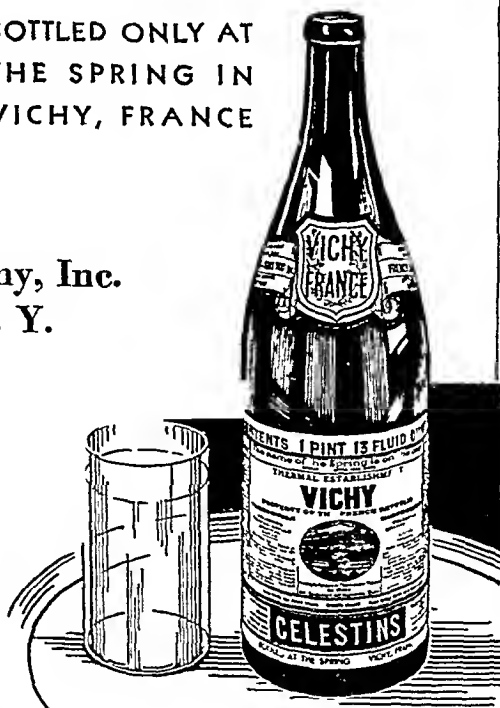
Sodium bicarbonate	3 3090
Potassium bicarbonate	0 2490
Lithium bicarbonate	0 0281
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Growth and Development of the Child, Part III, White House Conference on Child Health and Protection, New York, 1932, p 213

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many diets are acid-forming

ORDINARY cereals and cereal products, meat, and eggs—all produce an acid ash when burned in the body, yet they form the mainstay of the average diet. Although this preponderance of acid-forming foods is not definitely known to have great significance for the health of normal adults, a number of authorities advocate a basic or alkali-forming diet for children and pregnant women.

Infancy and Childhood. "Alkaline diets are essential for infancy where growth is rapid," declares Shohl. He calculates the need as 10 cc excess of 0.1 normal base per kilo per day.¹ Babies fed on breast milk stored an excess of base over acid, the range being from 31 to 56 cc 0.1 N base per day, is the finding of the Committee on Growth and Development of the White House Conference on Child Health.² Lippard and Marples observed greater increases in weight of infants receiving basic diets as compared with controls on acid-forming feedings.³

Pregnancy and Lactation. Shohl states, "Pregnancy and lactation require additional alkali—a minimum of 150 cc 0.1 N base per day."¹ Coons and associates, from acid-base balances taken upon normal pregnant women receiving basic diets, determined that the storage of basic substances was even greater than estimated by Shohl. "This may be some indication," they say, "of the magnitude of the maternal needs exclusive of fetus."⁴

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Wheat, whole		11.5
Cornmeal		5.3
Barley		10.1
Rice		8.1

Figures given in the above table are based on 100 grams of food and represent cubic centimeters of normal acid or base.

¹⁻⁴ Bibliography on request

*Mead's Cereal (Pablum in uncooked form) is also base forming

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ANNALS OF INTERNAL MEDICINE

VOLUME 11

OCTOBER, 1937

NUMBER 4

THE CLINICAL USE OF SULPHANILAMIDE AND ITS DERIVATIVES IN THE TREATMENT OF INFECTIOUS DISEASES*

By PERRIN H. LONG, M.D., and ELEANOR A. BLISS, Sc.D.,
Baltimore, Maryland

INTRODUCTION

THE experimental observations^{1, 2, 3, 4, 5, 6, 7} which have led to the use of sulphanilamide or its derivatives (chart 1) in the treatment of certain infectious diseases show that these chemicals have powerful chemotherapeutic effects in experimental infections. Clinical observations of their effects in human beings tend to confirm the laboratory results. In this communication we propose to discuss primarily the clinical application of these chemotherapeutic agents, and to detail the methods of their administration and the possible toxic effects which may become manifest in patients treated with sulphanilamide or its derivatives.

It is interesting to note that the first mention of these products in the medical literature was that of Foerster⁸ who reported that "Streptozon" (Prontosil) had shown a marked chemotherapeutic effect in a boy suffering from a generalized staphylococcal infection. This report was delivered to the Dusseldorf Dermatological Society on May 17, 1933. In the following year Grutz^{9, 10} reported that he had obtained good results in the treatment of toxic and septic erythemas by using "Prontosil" by mouth, and "Prontosil Solution" by the intravenous route. In the same year Veil¹¹ reported upon the use of "Prontosil Solution" in the treatment of "rheumatism."

Early in 1935 Gmelin¹² discussed the use of "Prontosil" and "Prontosil Solution" in the treatment of erysipelas in children and concluded that the results obtained were so satisfactory that extensive clinical trials were warranted. It is worthwhile to remember at this point that up until February 1935 no experimental data concerning "Prontosil" or "Prontosil

* Read at the St. Louis meeting of the American College of Physicians, April 20, 1937.
From the Department of Medicine, The Johns Hopkins Hospital, Baltimore, Maryland.
Our investigations have been made possible by a grant from the Chemical Foundation, Inc., of New York City.

Solution" had been reported. However, in that month, the first experimental report¹ was issued. It was accompanied by four more clinical papers dealing with the use of the dyes in various types of infectious processes^{13, 14, 15, 16}. These clinical reports dealt with the use of "Prontosil" and "Prontosil Solution" in the treatment of streptococcal thrombophlebitis, adenitis, otitis media, erysipelas, puerperal fever and infectious arthritis. In general, the therapeutic results obtained were good. However, there was a divergence of opinion as to the efficacy of these chemicals in staphylococcal infections, Anselm¹⁵ reporting favorable results, while Schreus¹⁴ was doubtful of their value.

Following these reports there were numerous communications in the German literature dealing with the use of "Prontosil" and "Prontosil Solution" in a variety of diseases. Imhauser¹⁷ reported that he had obtained good results when these agents were used in the treatment of infections due to *E. coli*. Recknagel¹⁸ believed that the chemicals were of value in pneumococcal and staphylococcal as well as streptococcal infections. Bingold¹⁹ reported a patient with Hodgkin's disease, who either was cured or developed a prolonged remission after treatment with "Prontosil". Einhauser²⁰ considered the drugs of great value in the treatment of sepsis, and Fuge²¹ found that all cases of pure streptococcal puerperal sepsis recovered after treatment with the "Prontosils". In his opinion staphylococcal infections were not benefited.

Roth²² found the drugs of value in hemolytic streptococcal infections, and Schranz²³ reported 60 patients ill with sepsis, treated with the "Prontosils," of whom 57 recovered. He advised that the chemicals be used as prophylactic agents before operative procedures in septic patients. Riecke²⁴ observed nine cases of purulent meningitis, all treated with these new compounds. Six of these cases had bacteria in cultures of their spinal fluid. Three of the nine patients recovered, but unfortunately, the author gave no data as to the spinal fluid findings in these patients. Scherber²⁵ used "Prontosil" in pemphigus vulgaris, and Kramer²⁶ reported good results from its use in 23 patients ill with erysipelas.

The first clinical report from France appeared in 1935. In that country, a product analogous to "Prontosil" called "Rubiazol" was being used. Vermelin and Hartemann²⁷ reported that they had treated patients with puerperal sepsis with "Rubiazol" by mouth and by the intravenous route since May 1935. Four of their patients developed severe reactions following the intravenous use of "Rubiazol" and one patient succumbed to the reaction. These observers considered the product with which they had been working as too toxic for further use. Following this report, Floch²⁸ described the good results that he had obtained in treating patients ill with tropical streptococcal lymphangitis with "Rubiazol". These patients were all treated with "Rubiazol" tablets by mouth. Lemierre, La Porte, Laudat and Daum²⁹ carefully studied the effects of "Rubiazol" upon the kidney which had been damaged by an acute hemorrhagic nephritis. They con-

cluded the drug did not augment existing renal impairment Meyer-Heine and Huguenin³⁰ studied the effects of the "Chlorohydrate of sulphamide-chrysoidine" in 150 patients ill with erysipelas Eight of these patients were infants all of whom recovered These observers noted no toxic effects and concluded that the chemical was a chemotherapeutic agent of great value Recently Bloch-Michel, Conte and Durel³¹ have reported that para-amino-benzene-sulphonamide and benzyl-para-amino-benzene-sulphonamide have shown very favorable therapeutic effects in the treatment of erysipelas While para-amino-benzene-sulphonamide was effective, these authors preferred to use the benzyl derivative Their results were striking as far as influencing the clinical course of the disease was concerned, and they reported no toxic effects from the use of the benzyl compound

The first experimental and clinical report concerning the use of the "Prontosils" in England was that of Colebrook and Kenny³ who, after preliminary tests in mice, applied these products to the treatment of puerperal fever In a carefully studied series of patients they noted, not only a remarkable therapeutic effect in many cases, but an actual lowering of the expected case fatality rate They stated that they had observed sulphemoglobinemia and mild renal irritation following the use of these drugs Later, in a more extended clinical report³² these observers concluded that the use of the "Prontosils" not only materially changed the clinical course of streptococcal puerperal infection, but also brought about a definite decrease in the expected case fatality rate These two papers by Colebrook and Kenny have served to bring the possibilities of these new chemotherapeutic agents to the attention of the English speaking physicians

Fouls and Barr³³ have recently described the beneficial effects of sulphanilamide in the treatment of puerperal sepsis These observers used large doses of the chemical, and but one of their 28 patients, of whom 11 had a septicemia, succumbed to her infection Their conclusions were that sulphanilamide had a marked chemotherapeutic effect and a low toxicity Peters and Havard³⁴ used sulphanilamide in the treatment of 150 patients ill with scarlet fever In the treated group, 35 per cent of the patients developed complications, while in an equally large parallel control group, 56 per cent of the patients developed complications This difference in the complication rate was considered statistically significant These observers noted but few toxic manifestations from the drug

In a preliminary report Schwentker, Gelman and Long³⁵ noted that sulphanilamide had a definite therapeutic effect in the treatment of meningococcal meningitis, and concluded that results obtained with chemotherapy seemed quite as good as those obtained by the specific antiserum Dees and Colston³⁶ have used sulphanilamide in the treatment of acute gonococcal urethritis and are "deeply impressed" with "the surprisingly prompt response to treatment" which they observed in the majority of their patients Hemtzelman and his associates³⁷ have recently reported favorable results

from sulphanilamide therapy in the treatment of a small series of Type III lobar pneumonia patients

We^{5, 38, 39, 40} have observed striking effects from the use of sulphanilamide and its dye derivatives in the treatment of experimental and clinical hemolytic streptococcal infections. Furthermore, we⁴⁰ pointed out, as did Rosenthal⁴² and Cooper, Gross and Mellon⁴³ that sulphanilamide had some therapeutic effect in the treatment of pneumococcal infections in mice. Recently we⁴¹ have observed that this chemical is effective in treating experimental *Cl. Welchii* infections in mice.

Thus, it seems that sulphanilamide, instead of being a chemotherapeutic agent specific for hemolytic streptococcal infections, is a drug possessing a broad chemotherapeutic valency. At the present time, enough experimental and clinical evidence exists to warrant the use of sulphanilamide or "Pron-tosil Solution" in the treatment of hemolytic streptococcal infections, and for the use of sulphanilamide in meningococcal infections. Its use in pneumococcal infection rests mainly upon experimental data which are not, as yet, conclusive. Clinical evidence alone supports the use of this chemical in gonococcal infections.

In evaluating the clinical effect of these new chemotherapeutic agents, in this report we will base our evidence solely upon the results obtained in the treatment of hemolytic streptococcal meningitis. It has been well recognized in the past⁴⁴ that this disease constituted an almost invariably fatal infection, with a case fatality rate of about 99 per cent. Hence, the reports of the case histories of patients recovering from this disease as the result of sulphanilamide therapy are of utmost importance in establishing the clinical value of sulphanilamide or its derivatives.

In 1936 Causse, Loiseau and Gisselbrecht⁴⁵ reported the first patient ill with hemolytic streptococcal meningitis who, after treatment with "Pron-tosil," made a complete recovery. This was followed by the report of Arnold⁴⁶ who treated a patient suffering from hemolytic streptococcal meningitis with sulphanilamide. Recovery took place promptly. Since this first report Arnold⁴⁷ has successfully treated five additional patients ill with hemolytic streptococcal meningitis. Shortly after Arnold's report, Schwentker and his associates⁴⁸ reported recoveries in three out of four patients ill with hemolytic streptococcal meningitis and treated with sulphanilamide. Subsequent to these reports, Anderson⁴⁹ has reported one case of streptococcal meningitis, and Weinberg and his associates⁵⁰ two cases of the same disease who have recovered after being treated with sulphanilamide or its derivatives.

In this report we will discuss the course and therapy in four additional patients ill with hemolytic streptococcal meningitis.

CASE REPORTS

Case 1 P. F., a seven year old white girl, was brought to the Harriet Lane Home of the Johns Hopkins Hospital in a comatose state on February 15, 1937.

Five weeks before entry into the hospital, she had had measles and a left ear ache. Four days before coming to the hospital, the child developed malaise, headache, fever and a left ear ache. Paracentesis of the left ear drum was performed and the ear discharged pus. On the day before entering the hospital, a headache and stiff neck appeared. Upon the morning of admission to Harriet Lane, the child was delirious and vomited. She became comatose while being brought to the hospital. The physical examination showed a comatose, moribund child. The pupils did not react to light, and there was a definite blurring of the nasal margin of the nerve head in the left eye. No mastoid swelling or stiffness of the neck could be elicited. Kernig's sign was negative. The remainder of the physical examination was essentially negative. Laboratory examinations: Urine, negative. Hemoglobin, 104 per cent. Sahl's, red blood cell count 5.4 millions, white blood cell count 38,200. Differential count, polymorphonuclears 45 per cent, juvenile polymorphonuclears 6 per cent, immature forms, 43 per cent, lymphocytes, 4 per cent. Cerebrospinal fluid, no increase in pressure, Pandy test 4 plus, white blood cells, 4,620, differential count, mononuclears 76 per cent, polymorphonuclears 24 per cent. Chains of gram positive cocci were seen in stained films of the cerebrospinal fluid. The Wassermann test was negative. Blood culture was negative. The culture of the cerebrospinal fluid showed a pure culture of Beta hemolytic streptococci. Cultures of the pus from the left external auditory canal showed Beta hemolytic streptococci, *Staphylococcus aureus* and *B. proteus*. Shortly after entry, 18 grams of sulphanilamide were administered by the parenteral route, and a transfusion of 80 c.c. of citrated blood was given. The patient died a few hours after entering the hospital.

Autopsy "The longitudinal sinus is open. The brain is normal except that the meninges over the median portion of the base of the cerebellum, over the medulla and pons and extending up to the Sylvian fissure and optic chiasm show a whitish opacity. On section the ventricles are normal. The brain substance looks normal." Bacteriological cultures of the meninges showed Beta hemolytic streptococci.

Case 2 W. H., a nine year old white boy, was admitted to the Johns Hopkins Hospital on February 14, 1937, complaining of bilateral ear ache. Late in December 1936, the patient contracted a severe cold accompanied by pain in the right ear. Soon pain developed in the left ear, and a bilateral paracentesis was done. Then the ears drained profusely. Drainage continued until February 10, 1937, at which time a severe chill occurred and the patient became quite ill. Four days later, he came to the Johns Hopkins Hospital. His temperature at this time was 105° F. On physical examination a profuse, bubbly, pulsating discharge was noted in both external auditory canals, and both ear drums were found to be perforated. There was no mastoid tenderness. His neck was stiff and his hearing poor. A roentgenogram showed clouding of the right mastoid cells. A simple bilateral mastoidectomy was performed. Following the operation 16 grams of sulphanilamide were given by the subcutaneous route, and sulphanilamide tablets grains 5 q 4 hours were started. The culture of the pus from the mastoid region showed Beta hemolytic streptococci. The immediate postoperative course of this patient was favorable. Upon the tenth day after operation, the boy's temperature became definitely elevated. A roentgenogram did not show evidence of osteomyelitis. Because of a continuation of fever, the left mastoid region was again explored on February 27, and exuberant granulation tissue was removed. The lateral sinus appeared normal. The fever, however, continued. The sulphanilamide was increased to grains 10 q 4 hours. A sulphanilamide blood level of 9 milligrams per cent was reached and maintained. Because, however, of continuation of fever, the petrous portion of the left temporal bone was explored on March 11 and 27, 1937. Following the last operation the patient became nauseated, and the drug was discontinued on March 30. By April 1, only a trace of sulphanilamide was found in the blood. Stiffness of the neck was again noted on March 31. A lumbar puncture showed a cloudy fluid containing 5,950 white

blood cells A culture of the spinal fluid showed Beta hemolytic streptococci Intensive sulphanilamide therapy by the subcutaneous and intrathecal routes was begun on April 1 The details of this therapy are shown in chart 5 Despite all therapeutic efforts, the child died on April 8

Autopsy The gross specimen of the brain was described as follows "The cerebral hemispheres show only a few little gray patches in the meninges There are definite streaks of exudate along the fissures of Sylvius on each side In the region of the cisterna magna, and over the inferior surface of the cerebellum, there is an extensive meningitis The exudate extends up around the lateral and on to the dorsal surface of the pons The lateral and third ventricles are a little widened, and contain a purulent exudate On section no abscesses are found" Bacteriological cultures of the exudate yielded Beta hemolytic streptococci

The method of therapy in this patient's case is shown in chart 1

CHART I

Case 2

Date April 1937	Time of Treat- ment	Sulphanilamide Therapy (grams)			Cerebro-Spinal Fluid		Remarks
		In- tra- the- cal	Sub- cutan- eous	Per Os	W B C	Culture	
1	4 30 p m	0 135	3 2			B H S	150 c c 1/6 Molar Na Lactate Sc
	11 45 p m	0 135	1 6		1,040	B H S	
2	9 30 a m	0 16	2 4		120	B H S	Blood Sulphanilamide = 10 3 mg % CSF Sulphanilamide = 11 1 mg % CO = 52 Vols % Hgb 80% CSF Sulphanilamide = 15 75 mg % 150 c c 1/6 Molar Na Lactate Sc
	5 30 p m	0 24	2 4		8,200	B H S	
3	1 a m	0 16	2 4		1,048	B H S	CSF Sulphanilamide = 24 4 mg % CSF Sulphanilamide = 25 mg % CSF Sulphanilamide = 18 2 mg %
	10 30 a m	0 32	2 4		650	B H S	
	7 p m	0 28	1 6		508	B H S	
4	3 00 a m	0 20	2 4		620	B H S	CSF Sulphanilamide = 16 mg % Blood Sulphanilamide = 8 7 mg % Transfusion 200 c c
	11 30 a m	0 32		3 6	2,040	B H S	
	7 30 p m	0 28			1,180	B H S	
5	3 00 a m	0 12			1,240	B H S	CSF Sulphanilamide = 10 mg % Blood Sulphanilamide = 8 mg % CSF Sulphanilamide = 8 mg %
	11 30 a m	0 16		1 8	620	B H S	
	7 30 p m	0 12			636	B H S	
6	3 30 a m	0 12	2 4			B H S	CSF Sulphanilamide = 13 7 mg % CSF Sulphanilamide = 11 25 mg % CSF Sulphanilamide = 16 25 mg %
	1 00 p m	0 24	2 4	1 8		B H S	
	8 30 p m	0 2	2 0		1,020	Neg	
7	3 00 a m	0 12				B H S	CSF Sulphanilamide = 12 mg % CSF Sulphanilamide = 14 mg % CSF Sulphanilamide = 14 mg % Blood Sulphanilamide = 11 2 mg % 150 c c 1/6 Molar Na Lactate Sc
	11 00 a m	0 12	2 0			B H S	
	8 30 a m	0 12	2 4		11,200	Neg	
8	3 00 a m	0 12				B H S	CSF Sulphanilamide = 22 7 mg % CSF Sulphanilamide = 14 1 mg % Hematocrit 40% Icterus Index 15 Respiration ceased
	12 30 p m	0 16	2			Neg	
	7 45 p m						

Case 3 I S This 47 year old woman was a patient in the Spring Grove State Hospital, Maryland Upon April 7, 1937, she was transferred to the hospital infirmary because the glands of her neck were swollen, and both ears were draining freely Her subsequent course is shown in chart 2

CHART II

Case 3

Date April 1937	Time of Treatment	Sulphanilamide Therapy (grams)			Cerebro Spinal Fluid		Remarks
		In-trathe-cal	Sub-cutaneous	Per Os	W B C	Culture	
8				0.3			Temp 103.6 to 104.6 80 c c Prontosil solution s c Soda bicarb 30 grains per os
9							Temp 99 to 104 No therapy Both ears draining slightly
10				0.3			Temp 100 to 101
11							Temp 99.4 to 100 No therapy Both ears draining slightly
12	5 p m	0.12			1900 P (a m) 3800 P (p m)	Strep (smear only)	Temp 103 to 106 40 c c Prontosil solution s c at noon Blood culture = no growth
13	1 a m 10 a m 4 p m 5 p m	0.08 0.08 0.08	2.4 2.4 2.4	0.66	1630 P (a m) 1020 P (a m)	B H S (33 cols) B H S (2 cols)	Temp 102 to 104
14	1 a m 7 a m 10 a m 1 p m 5 p m 6 p m 9 p m	0.08 0.08 0.08 0.8	2.4 2.4 2.4	1.3 1.3 1.3	1560 P (a m)	No growth	Temp 100 to 103 Soda bicarb 40 grains per os
15	1 a m 8 a m 11 a m 1 p m 6 p m 9 p m	0.2 0.2 0.04	2.4 2.4	1.3 1.3 1.3	2900 (a m) (P=85% L=10% M=5%)	B H S (6 cols)	Temp 99.6 to 103.2 Soda bicarb 10 grains per os
16	1 a m 8 a m 11 a m 1 p m 6 p m 8 p m	0.12 0.12	2.4 2.4	1.3 1.3 1.3	2360 (a m) P=90% L=8% M=2%	No growth	Temp 100 to 103.4 Resp 28 to 52 Soda bicarb 50 grains per os CO ₂ combining power = 24.8 vols per cent at 6 p m
17	2 a m 9 a m 5 p m 9 p m	0.12 0.07 0.12	2.4 2.4	1.3 1.3			Temp 101.2 to 105.6 Resp 36 to 60 900 $\frac{M}{6}$ Na lactate at 4 p m Soda bicarb 100 grains per os at 9 p m CO ₂ combining power = 15.5 vols per cent in the morning
18	1 a m 12 N 2 p m 5 p m 10 p m	0.12 0.2 0.12		1.3 1.3 1.3		No growth	Temp 99.4 to 102.6 Resp 48 to 56 Soda bicarb 250 grains per os CO ₂ combining power = 36.9 vols per cent at 2.45 p m
19	8 a m 10 a m 2 p m 6 p m	0.16		1.3 1.3 1.3	775	No growth	Temp 100 to 102.8 Resp 40 to 56 Soda bicarb 150 grains per os CO ₂ combining power = 59.1 vols per cent Hgb = 53% R b c = 2.6 W b c = 21 000

P—Polymorphonuclear neutrophils L—Lymphocytes M—Monocytes B.H.S.—Beta hemolytic streptococci s.c.—subcutaneously Temp—axillary temperature in degrees Fahrenheit

CHART II—Continued

Date April 1937	Time of Treatment	Sulphanilamide Therapy (grams)			Cerebro-Spinal Fluid		Remarks
		In-trathe-cal	Sub-cutaneous	Per Os	W B C	Culture	
20	8 a m 9 a m 10 a m 2 p m 6 p m	0 16		1 3 1 3 1 3 1 3	220 (a m)	No growth	Temp 99 6 to 100 8 Resp 36 to 46 Soda bicarb 150 grains per os Hgb = 49% R b c = 2 3 W b c = 17 000
21	9 a m 11 a m 3 p m 10 p m	0 2		1 3 1 3 1 3			Temp 99 4 to 101 2 Resp 32 to 48 Soda bicarb 150 grains per os Hgb = 50% R b c = 2 3 W b c = 24 000
22	10 a m 12 N 1 p m 7 p m 8 p m	0 16		0 66 0 66 0 66 0 66			Temp 99 to 101 2 Resp 34 to 42 Soda bicarb 110 grains per os Hgb = 40% R b c = 2 4 W b c = 19 000
23	1 a m 11 a m 8 p m			0 66 1 3 0 66			Temp 99 to 100 8 Resp 32 to 36 Soda bicarb 95 grains per os Transfusion 600 c c citrated blood at 6 p m
24	10 a m 2 p m 10 p m			1 0 1 0 1 0			Temp 98 6 to 99 8 Resp 20 to 38 Soda bicarb 110 grains per os Hgb = 58% R b c = 3 1 W b c = 15 700
25	9 a m 10 a m 3 p m 10 p m			1 0 1 0 1 0 1 0			Temp 98 2 to 99 8 Resp 24 to 38 Soda bicarb 40 grains per os
26	11 a m 6 p m 10 p m			1 0 1 0 1 0			Temp 99 2 to 100 2 Resp 24 to 30 Soda bicarb 150 grains per os Hgb = 65% R b c = 3 2 W b c = 9200
27	1 p m 6 p m 10 p m	0 16		1 0 1 0 1 0	470	No growth	Temp 99 2 to 100 2 Resp 28 to 36 Soda bicarb 40 grains per os CO combining power = 59 1 vols per cent Hgb = 67% R b c = 3 2 Retic 7 6% W b c = 8000 Urine sterile
28	3 times a day			Total 3 0			* Temp 98 8 to 99 Resp 24 to 32 Soda bicarb 40 grains per os
29	4 times a day			Total 4 0			Temp 99 to 100 6 Resp 24 to 28 Soda bicarb 40 grains per os
30	4 times a day			Total 4 0			Hgb = 65% R b c = 3 2 W b c = 7400
May 1-13	4 times a day			Total 4 0 per diem			Soda bicarb 40 grains per os per diem
13-27	4 times a day			Total 3 0 per diem			Soda bicarb 30 grains per os per diem
13							Hgb = 60% R b c = 3 3 W b c = 13 300

Case 4 J E B Sydenham Hospital, Baltimore City Health Department A three year old white boy entered the hospital on March 25, 1937, because of measles and pncumonia His older brother and sisters had had measles On March 18, the patient developed a cold, followed on the next day by a typical mcasles rash Three days later, the child had difficulty breathing, a physician was called, and a diagnosis of pneumonia was made The boy was removed to the hospital Upon admission, he showed a fading measly eruption, no Koplik spots, and dullness and crepitant rales over the right lung field Within a week after entry in to the hospital, the child had made a marked improvement However, on April 7, his ears drained spontaneously, and a spiking fever appeared This continued and because of a secondary anemia, he was given two transfusions of 100 c c of citrated blood on April 26

and 27 Just prior to the transfusions, on April 22, the child's red blood cell count was 3.2 millions, and his hemoglobin 52 per cent. He did not improve following the transfusions, and on April 26, it was noted that his neck was stiff. A lumbar puncture was performed, and gram positive diplococci were seen in the stained film of the cerebrospinal fluid sediment. The subsequent course of the patient is shown in chart 3.

CHART III

Case 4

Date April 1937	Sulphanilamide Therapy (grams)			Cerebro-Spinal Fluid		Remarks
	Intra- the- cal	Subcu- tane- ous	Per Os	W B C	Culture	
28	0.2	2.0		3750 75% Polys	B H S	Ears draining, culture = B H S Neck stiff
29	0.23	3.0 2.0		2525 82% Polys	B H S	Neck stiff
30	0.2 0.2 0.2	2.0 3.0 3.0		1175 75% Polys	Sterile	Able to bend neck
May 1	0.15	3.0 2.0		570 60% Polys	Sterile	Markedly improved
2		2.0				Temperature normal upon 5/4/37
14				140 30% Polys		Discharged from hospital 5/15/37

In reviewing the events in the histories of these four patients, it is evident that the first patient was moribund upon entry into the Harriet Lane Home and was beyond all therapeutic aid. The second patient represents a definite failure of sulphanilamide therapy for which we have no adequate explanation. It has been our experience that hemolytic streptococcal otitis media is very responsive to treatment with this chemical. This is also true of the postoperative course of patients ill with acute hemolytic streptococcal mastoiditis, in whom sulphanilamide therapy has been instituted. However, in this instance there was a definite progression of the streptococcal infection despite supposedly adequate therapy with sulphanilamide. Whether the discontinuance of the drug on March 30 permitted the streptococci to invade the spinal fluid is a matter of conjecture, but it is interesting to note that within 36 hours the first signs of meningitis appeared, and at that time less than 1 milligram per cent of sulphanilamide was present in the blood of the patient. However, the institution of adequate therapy did not influence the course of the disease despite the fact that the streptococci isolated from this patient were susceptible *in vitro* to the bacteriostatic effects of sulphanilamide.

The record of the third patient definitely demonstrates what may happen if therapy is discontinued too soon. In this instance, on the fourth day after treatment was stopped, the meningeal invasion took place. The effect of not adding base to the sulphanilamide therapy is also beautifully illustrated in this case, by the drop in the CO_2 combining power to 15.5 volumes per cent after 111 hours of treatment. Then with intensive alkali therapy, a normal CO_2 combining power was soon reestablished.

The final case is of importance in showing the effect of neglecting specific therapy in the presence of a hemolytic streptococcal otitis media. This patient also illustrates the rapid and uneventful course to recovery that is being increasingly noted in hemolytic streptococcal meningitis since the introduction of sulphanilamide therapy.

In addition to these recorded cases of hemolytic streptococcal meningitis, we have been consulted in regard to nine other patients ill with this disease, eight of whom have recovered. Thus, from our own experience and that recorded in the literature, we have knowledge of 28 cases of streptococcal meningitis occurring within the last 16 months. All were treated with sulphanilamide or its derivatives. Twenty-four or 85 per cent recovered. This recovery rate is to be contrasted with a case fatality rate of 99 per cent before sulphanilamide therapy was used in hemolytic streptococcal meningitis. This constitutes irrefutable evidence of the value of sulphanilamide therapy in the treatment of severe Beta hemolytic streptococcal infections in human beings.

THE TOXIC MANIFESTATIONS OF SULPHANILAMIDE AND ITS DERIVATIVES

Sulphanilamide is a toxic chemotherapeutic agent, and its widespread employment will result in many fatalities unless the tendency towards its careless and reckless use is checked. Already fatalities attributed to the use of sulphanilamide or its derivatives have been reported⁵¹ and we have seen one instance in which death was associated with a toxic effect of sulphanilamide.

The most serious toxic manifestations of sulphanilamide therapy are those associated with the blood or hematopoietic system. We have seen seven patients who developed acute hemolytic anemias characterized by a sudden fall in the hemoglobin and red blood cell count, and the appearance of macrocytosis, anisocytosis, poikilocytosis, elevated white blood cell counts, nucleated red blood cells and large numbers of reticulocytes in the peripheral blood. Six of the seven patients were definitely jaundiced, and in all a marked urobilinuria was present. All of these patients recovered promptly, but in five the anemia was so severe as to necessitate one or more transfusions.

The mechanism of the production of these anemias is as yet unknown, but it does not seem to be of the nature of a true idiosyncrasy because in two of the recovered patients the subsequent administration of test doses

of sulphanilamide did not result in any change in their red blood cells. Also, there has been no correlation between the amount of sulphanilamide administered and the development of anemia. It is probable that the anemias represent an abnormal susceptibility on the part of the red blood cells of certain individuals to severe hemolysis by sulphanilamide.

Another severe toxic effect of sulphanilamide has been the development of granulocytopenia. Plumer⁵² has reported a patient who developed this toxic manifestation while under treatment with sulphanilamide. Despite the discontinuance of the drug, the patient died. In two instances Trumper⁵³ has seen definite leukopenias associated with a depression of the myeloid elements appear in patients who were being treated with sulphanilamide and "Prontosil Solution". We have seen one patient in whom death was associated with a granulocytopenia combined with a bilateral, lateral and cavernous sinus thrombosis. During the month before death, this patient had received irregular medication with "Prontosil Solution" and sulphanilamide. Recently, we have observed a patient who had made a rapid recovery from a gonococcal urethritis and arthritis as the result of sulphanilamide therapy. At the end of the third week of treatment he developed weakness, slight jaundice and a sore throat. Upon reentry into the hospital he was found to have a mild anemia and a leukopenia associated with a marked depression of the myeloid elements. An extensive angina was present. No specific therapy was used and within 10 days the patient's blood picture was normal. He was then given two test doses of sulphanilamide, the first 0.3 gram, the second 2.0 gram by mouth, without showing any depression of his white blood cells. It seems, from this lack of response to the test dose, that the mechanism of the production of granulocytopenia by sulphanilamide differs from that by amidopyrine.

In addition to the severe toxic manifestations just described, sulphanilamide produces certain mild clinical toxic effects. In normal human beings, the ingestion of 50 grains of sulphanilamide is followed in six hours by slight dizziness and mild nausea. Ambulatory patients who are suffering from streptococcal or gonococcal infections often complain of dizziness, anorexia, nausea and sometimes of a sensation which is described as being similar to that experienced when mildly intoxicated with ethyl alcohol. These effects, however, are rarely noted in patients who are kept in bed during the period of therapy.

Practically every patient who receives sulphanilamide in therapeutic doses shows a fall in the CO_2 combining power of the blood. We have seen four cases of clinical acidosis, characterized by air hunger, and a very alkaline urine without ketonuria, which have developed in the course of sulphanilamide therapy. This toxic manifestation of the drug has been studied in the medical clinic of the Johns Hopkins Hospital by Southworth⁵⁴ who noted that a variable but consistent drop in the CO_2 combining power of the blood plasma occurred in 15 consecutive cases of streptococcal infec-

tion which had been treated with sulphanilamide. We have found that this fall in the CO_2 combining power of the blood plasma is associated with an absolute loss of sodium and potassium in the urine. This loss of base varies markedly in different individuals. Certain patients have a mechanism that permits them to control this loss of base before they develop a clinical acidosis. The exact method of the control of this excretion of base during sulphanilamide is under study at the present time. We have found that the administration of 10 grams of bicarbonate of soda with each dose of sulphanilamide is of value in preventing the fall in the CO_2 combining power, and at the present time we administer bicarbonate of soda routinely with each dose of sulphanilamide.

If acidosis should develop, the administration of 1/6 molar sodium lactate solution by the intravenous and subcutaneous routes is of definite value in combating this toxic manifestation of sulphanilamide therapy. In babies, frequent small hypodermoclyses of 1/6 molar sodium lactate solution may be used to prevent acidosis.

Sulphanilamide may cause fever. When this occurs, it is best to stop the drug for two or three days during which period the temperature will fall to normal if the fever is due to the sulphanilamide therapy.

We have carefully studied the urine of patients receiving sulphanilamide without noting signs of renal irritation. As we have stated previously, sulphanilamide is not excreted rapidly by the damaged kidney, and hence it tends to accumulate in the blood of patients having decreased renal functions. We believe that if the drug is to be used in patients with decreased renal function, the sulphanilamide blood levels should be followed daily. When the blood sulphanilamide level reaches 15 to 20 mg per cent, the drug should be stopped.

Schwentker⁴⁵ and ourselves have noted morbilliform skin rashes accompanied by fever, which appeared in the course of sulphanilamide therapy. These rashes generally develop from the eighth to fourteenth day of treatment. When such skin eruptions develop, sulphanilamide therapy should be discontinued, and the rash and fever will disappear within 48 hours.

In patients suffering from the acute toxic manifestations of sulphanilamide therapy, we have found that large amounts of fluids act as an antidote. We have seen one patient who took 12 grams of sulphanilamide within 12 hours and who developed headache, dizziness, nausea and a moderate degree of cyanosis. Inasmuch as we know that the chemical is excreted with water, we had this patient force fluids to the extent of taking 5,000 cc of water by mouth within a six hour period. The drug was rapidly excreted, and after a few hours, all signs of toxicity disappeared.

Colebrook and Kenny³ reported that the "Prontosils" had a mildly irritative effect upon the kidney, and that these compounds produced sulphemoglobinemia in three of their patients. They believed, however, that the association of saline cathartics with the therapeutic administration of the

"Prontosils" was a contributing factor in the production of the sulphemoglobinemia, and advised against the use of saline cathartics in patients receiving "Prontosil"

In our experience "Prontosil Solution" has produced but one toxic effect, namely, fever. This manifestation appears constantly in those normal subjects who have been tested with a single large dose (100 cc) given by the subcutaneous route. It also occasionally is seen on the third day or later of continuous "Prontosil Solution" therapy. It is our practice to discontinue "Prontosil Solution" if fever appears which is considerably out of proportion to the general clinical condition of the patient. As this generally occurs at a time when the streptococcal lesion is rapidly regressing, the clinical problem is not difficult. We have not seen any evidence of renal irritation in patients receiving "Prontosil Solution."

METHODS OF ADMINISTRATION OF SULPHANILAMIDE OR ITS DERIVATIVES

Our experience leads us to believe that sulphanilamide per os is the drug of choice. If, however, the patient cannot swallow tablets, or oral administration of sulphanilamide is not desirable, we use either "Prontosil Solution" or an 0.8 per cent to 1 per cent solution of sulphanilamide in sterile physiological saline solution. These solutions are given parenterally by the subcutaneous route.

In our previous communication⁵ we came to the conclusion based on our knowledge that a 1-10,000 concentration of sulphanilamide was definitely bacteriostatic in vitro, that this would constitute an effective therapeutic level in vivo. Our earlier system of dosage was, therefore, based upon amounts of sulphanilamide which would theoretically give us this concentration.

Recently, Dr. E. K. Marshall, Jr., and his associates^{56, 57} have described a simple biochemical method for the quantitative determination of sulphanilamide in body fluid. They have noted, following a single oral dose in human beings, that the drug is absorbed in about four hours, and that a maximum concentration is reached in the blood stream within four to six hours. They demonstrated that the drug is almost wholly excreted in the urine and that this is accomplished rapidly by the normal kidney. In patients with decreased renal function, Marshall found a diminished ability to excrete sulphanilamide, and noted that the continued ingestion of the chemical in these patients resulted in an accumulation of the drug in the body. It was also noted that the drug rapidly passed over into all body fluids in approximately the same concentration as was found in the blood. These observations have been of the greatest importance in establishing a rational basis for therapy in infected human beings.

Therefore, in patients ill with very severe infections, such as hemolytic streptococcal meningitis, peritonitis and septicemia, or in meningococcal meningitis or septicemia we believe that because of the gravity of the prog-

nosis in such diseases, one should disregard all possible toxic effects of sulphanilamide or its derivatives in an attempt to control the infections as rapidly as possible. This we do by administering a large initial dose of sulphanilamide with the aim of attaining a blood level of 10 mg per cent within four hours. In adult patients, i.e. those weighing 100 pounds or more, we administered an initial dose of from 10 to 16 five grain tablets. This initial dose should give a blood level of about 10 mg per cent within four hours. Then, to maintain this level, we advise using three 5 grain tablets every four hours. If the patient weighs 50 to 90 pounds, the initial dose should be 6 to 10 five grain tablets followed by two or three tablets at four hour intervals. In children weighing from 25 to 50 pounds, four to six 5 grain tablets constitute the initial dose, followed every four hours by doses of one or two 5 grain tablets. Patients excrete the drug at slightly different rates, so the maintenance dose may vary somewhat.

We have found it advantageous to determine the blood sulphanilamide level four hours after the initial dose. If the blood does not show the expected level of 8 to 10 mg per cent, this is evidence of faulty absorption, and the parenteral administration of the chemical should be instituted. It is of value to check the blood sulphanilamide level 24 hours after therapy has been started, to determine the adequacy of the maintenance dose of the drug.

The preparation of sulphanilamide for parenteral use is simple. This chemical is soluble up to 1 per cent in physiological saline solution at 37° C. It is our practice to bring the required amount of sterile physiological saline solution to a boil. It is then removed from the flame, and as soon as it stops boiling, 0.8 to 1 gram of sulphanilamide is added for each 100 c.c. of physiological saline solution. The hot saline solution is then agitated to facilitate the solution of the sulphanilamide, cooled to 37° C. and is administered by hypodermoclysis. A 1 per cent solution of the drug will remain fairly stable if kept at room temperature. If the temperature falls, or if the solution is placed in an ice box, the sulphanilamide crystallizes out of solution. It is our custom to make up the daily requirements of sulphanilamide solution for a patient each morning.

Our experience in the use of parenteral sulphanilamide solution leads us to believe that the following amounts represent adequate therapeutic doses. In adults, the initial hypodermoclysis should be 500 c.c. of a 1 per cent solution, followed by 300 c.c. at eight hour periods during the first 24 hours. The initial dose for individuals weighing from 50 to 90 pounds should be from 200 to 400 c.c. followed by 200 c.c. at eight hour intervals. Children weighing 25 to 50 pounds should receive an initial dose of 100 to 300 c.c. of sulphanilamide solution, this to be followed with 100 to 200 c.c. of the solution at eight hour intervals. In babies, it is difficult to determine the dose, but they should receive a total of 1 gram of sulphanilamide per 10 pounds of body weight during the first 24 hours.

Sulphanilamide solutions may be given by the intrathecal route in the treatment of streptococcal infections of the meninges. The drug has not been found irritating to the meninges, and the technic of administration is the same as that used in giving antisera by this route. The solution is warmed to 37° C and after the spinal drainage has been completed, an amount of sulphanilamide solution equivalent to 5 or 10 c c less than the amount of cerebrospinal fluid which has been removed, is permitted to run into the spinal canal under the force of gravity. Never inject the solution under *positive pressure*. Intrathecal therapy may be given at eight hour periods in infections of the meninges.

"Prontosil Solution" should be given by the subcutaneous route. It is absorbed rapidly and is practically non-irritating. For two or three minutes after its injection, a sensation of burning or stinging may be noted at the site of injection. This may be obviated by infiltrating the area of injection with a small amount of a local anesthetic. The drug is absorbed rapidly, and has been noted in the urine within 15 minutes after a single subcutaneous injection of 100 c c of the solution. Because of the frequency with which the drug is given, we start its administration in the right pectoral region and proceed to the left pectoral region, then to the outside, top and inside of both thighs, and next to each of the buttocks. Following the injection in the buttocks, one may return to the right pectoral region.

In adults, the therapeutic dose of "Prontosil Solution" is 20 c c at four hour intervals or a total of 120 c c of the solution in 24 hours. Individuals weighing 50 to 90 pounds should receive from 10 to 15 c c of the drug at four hour intervals. Children weighing from 10 to 50 pounds should receive 5 to 10 c c every four hours. These doses should be continued in each instance until a definite clinical effect has been obtained. Then the dose may be gradually decreased. It will be noted that doses of "Prontosil Solution" such as we have recommended will color the skin pink and the urine bright red. "Prontosil Solution" is definitely irritating when given intrathecally, and should not be administered by this route. Severe reactions may occur after the intravenous administration of the drug.

After definitely favorable clinical effects in the patient have been obtained, the dose of sulphanilamide should be rapidly decreased. At first, the dose may be cut by one-third. Then if the improvement in the patient's condition is continued, the drug should be cut to one-third of the original amount. This should be continued until convalescence is well established.

Up to this point, we have discussed only the maximum dosage which is to be used in very severe streptococcal or meningococcal infections. Moderately severe streptococcal infections in adults may be controlled by the administration of three 5 grain tablets of sulphanilamide at four hour intervals. Mild streptococcal infections may be combated with one or two tablets at four hour intervals. In children, one or two tablets every four hours constitutes an effective dose. As soon as a definite clinical improvement is

noted, the amount of sulphanilamide should be decreased. If a recurrence of the infection occurs, or if clinical improvement is not seen after 36 hours of sulphanilamide therapy, the therapeutic dose of this substance should be increased.

Sulphanilamide can be used as a prophylactic agent in the prevention of streptococcal infections, especially in the face of epidemic outbreaks. In adults two 5 grain tablets three or four times a day constitute the prophylactic dose, while in children one tablet three times a day appears to be sufficient.

SUMMARY

1 Clear experimental and clinical evidence is available which leads us to believe that sulphanilamide and its derivatives constitute powerful chemotherapeutic agents in the treatment of hemolytic streptococcal infections.

2 Experimental and clinical data support the use of sulphanilamide in meningococcal infections.

3 The clinical results obtained in treating gonococcal infections have been favorable.

4 Sulphanilamide has certain serious toxic effects upon the hematopoietic system.

5 The careless and reckless use of sulphanilamide is unwarranted, and will undoubtedly result in fatalities.

We wish to thank Dr E A Park, Dr Frances F Schwentker and Dr Herbert Harms for their courtesy in making the records of certain patients available to us.

The "Prontosil Solution" used in these experiments was supplied by the Winthrop Chemical Company. The sulphanilamide was supplied by the Abbott Laboratories, Lederle Laboratories, Merck and Company, Inc, E R Squibb and Sons, the Myron L Walker Company and the Winthrop Chemical Company.

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THE HEREDITARY FACTOR IN ESSENTIAL HYPERTENSION ~

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EVEN before facilities were available for measuring the blood pressure it was observed that vascular disease occurred with unusual frequency among members of some families. In 1769, Morgagni recorded cases of apoplexy and said that he believed the condition was influenced by hereditary factors in these cases because many near relatives of the patients had been afflicted with a similar ailment. In 1872, Gull and Sutton reported a group of cases of chronic interstitial nephritis and expressed the opinion that the disease in these cases was due to an arteriocalillary fibrosis throughout the body rather than the result of a lesion in the kidneys. They commented on the hereditary nature of the disease in this group of cases. Janeway, in 1916, wrote "The belief in an inherited quality of the arterial tissue with a tendency to premature death from apoplexy, angina pectoris and other local manifestations, is too firmly grounded in clinical observation to be without basis. Hypertensive arterial disease must be looked on to-day as the type in which heredity plays the largest rôle." These conclusions were derived mainly from scattered reports of human pedigrees and from casual clinical observations. It is only within the past 15 years that investigations of this problem have been of sufficient scope to be of significance.

The problem of the hereditary factor in hypertensive disease has been studied for the most part by three methods: (1) by observing and recording the histories of families in which vascular disease or hypertension has affected many members, (2) by investigating the family history as to the incidence of hypertensive cardiovascular disease among those who have or have had hypertension or a normal blood pressure, (3) by a study of the blood pressure of members of hypertensive and nonhypertensive families.

Weiss, Rosenbloom, Waldbott, Ayman and Étienne and Richard have studied the history of two or more generations of certain families in which an elevated blood pressure was found among a large number of the members. Ayman's report is especially significant as the blood pressure of three generations (32 members) of one family was measured.

Janeway obtained a history of familial cardiovascular disease from 50 per cent of a group of patients with hypertension. Popper studied 1,031 cases of hypertension and concluded that the hereditary factor was important. In studying the significance of an elevated blood pressure among young persons, Frost obtained a positive family history of cardiovascular disease from 28 per cent of 400 young adults who had an elevated blood pressure. Barach, in an especially detailed study of a small group of cases

* Presented at the St. Louis meeting of the American College of Physicians, April 20, 1937.

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of hypertension obtained a family history of cardiovascular disease in 95 per cent. He called attention to the incomplete information obtained from the family histories taken in the routine manner. I have found this to be true and in many instances have secured additional information by detailed questioning. A general question as to whether the patient knows of any hypertension or cardiovascular disease among his relatives elicits poor information. A direct question concerning the state of the blood pressure, heart, kidneys and cerebrovascular system of each near relative will result in a surprising amount of additional information.

Data concerning the incidence of hypertensive cardiovascular disease among relatives of persons who have hypertension and relatives of persons who have a normal blood pressure are of more significance than are similar data concerning only the relatives of persons who have hypertension. O'Hare, Walker, and Vickers found that 68 per cent of 300 patients who had hypertension gave a family history of cardiovascular disease, as compared with 37 per cent of 564 patients who did not have hypertension. They concluded that heredity undoubtedly plays one of the most important rôles in the production of hypertensive disease. Glomset measured the blood pressure of 2,400 school children and found a positive family history among 39 per cent of the children who had an elevated blood pressure and among 10 per cent of the children who had a normal or low blood pressure.

Since medical information concerning relatives usually is incomplete, measurement of the blood pressure of relatives gives more reliable information than does a study of the family history. Weitz has measured the blood pressure of brothers and sisters of hypertensive and nonhypertensive persons. He found that the incidence of elevation of the blood pressure was significantly higher among siblings of persons who had hypertension than it was among siblings of persons who did not have hypertension. The most extensive and significant study of this type has been made by Ayman.² He studied the blood pressure of 1,524 members of 277 families and found that in the families in which both parents had absolutely normal blood pressures the incidence of elevated blood pressures among the children was only 3 per cent. In the families in which one parent had arteriolar hypertension the incidence rose to 28 per cent and in families in which both parents had arteriolar hypertension the incidence was 45 per cent. Ayman found that the so-called emotional hypertension of young adults occurred almost wholly among the children of hypertensive families. He confirmed Weitz' studies in regard to the higher incidence of elevated blood pressure among siblings of persons who had essential hypertension.

RATIONALE OF PRESENT STUDY

Previous investigations of the hereditary factor in essential hypertension have been unavoidably deficient because high blood pressure becomes evident at varying ages, usually in later adult life, and because many persons

who have essential hypertension have frequent periods during which the blood pressure will be found to be normal. The emotional stimulus of taking the blood pressure often is not sufficient to cause a maximal elevation of the blood pressure or to bring out a latent hypertension. This can be demonstrated by a comparison of the blood pressure obtained at the first examination and that taken after the application of a strong external, sensory stimulus, such as ice water. I have collected a group of 90 cases in which there were hypertensive changes in the retinal arterioles, in these cases the values for the blood pressure, which was taken in the office, were always less than 150 mm of mercury for the systolic pressure and 95 mm for the diastolic pressure and frequently were normal or low. On application of a cold stimulus the value for the blood pressure would increase from 20 mm to 60 mm of mercury higher than the readings taken in the office. In these cases, the emotional stimulus of taking the blood pressure is not sufficient to bring out a latent hypertension. In 608 cases I have studied the blood pressure before and during the application of a cold stimulus. In 43 per cent of the cases the values for systolic and diastolic blood pressures were 10 mm of mercury higher during the application of the cold stimulus than they were on any reading before the application of the stimulus. In 8 per cent of the cases this increase amounted to 20 mm or more of mercury. In 5 per cent of the cases the initial values were less than 120 mm of mercury for the systolic pressure and less than 70 mm for the diastolic pressure but the value for the systolic pressure increased to more than 145 mm of mercury during application of the cold stimulus and the value for the diastolic pressure increased to more than 90 mm. Furthermore, it was found that from an emotional stimulus alone the elevation of blood pressure may be only in the systolic blood pressure, apparently as a result of cardiac stimulation rather than the result of vasoconstriction. Such emotional reactions of the blood pressure are of questionable significance if they are to be compared with the reactions in essential hypertension.

Hyperreactivity of certain portions of the arterial system is generally recognized as an important agent in producing the abnormality of the blood pressure which occurs in essential hypertension. A reliable method of measuring vasomotor reactivity, which does not depend on an emotional response and which would bring out a latent hypertension at each examination, should supply more complete information than has been obtained in previous studies of the hereditary factor in essential hypertension. The cold pressor test is believed to fulfill these requirements adequately.⁹ The technic of the test is as follows. The subject is allowed to rest in a supine position in a quiet room for 20 to 60 minutes. Thirty minutes is a satisfactory rest period for persons who have a normal blood pressure. If hypertension is present, a longer period of rest may be necessary to establish a basal level. Several readings of the blood pressure are taken until a basal level has been approximated. The cuff of the sphygmomanometer is placed

on one arm of the subject and his hand is placed in ice water (4°C) to a point just above the wrist. Readings of the blood pressure are taken at the end of 30 seconds and again at the end of 60 seconds. The maximal reading obtained while the hand is in the ice water is taken as an index of the response. The hand is removed from the ice water and readings are taken every two minutes until the blood pressure returns to its previous basal level. The maximal response frequently occurs within 30 seconds. The blood pressure of subjects who have a normal blood pressure returns to the basal level within two minutes. In the presence of established hypertension there

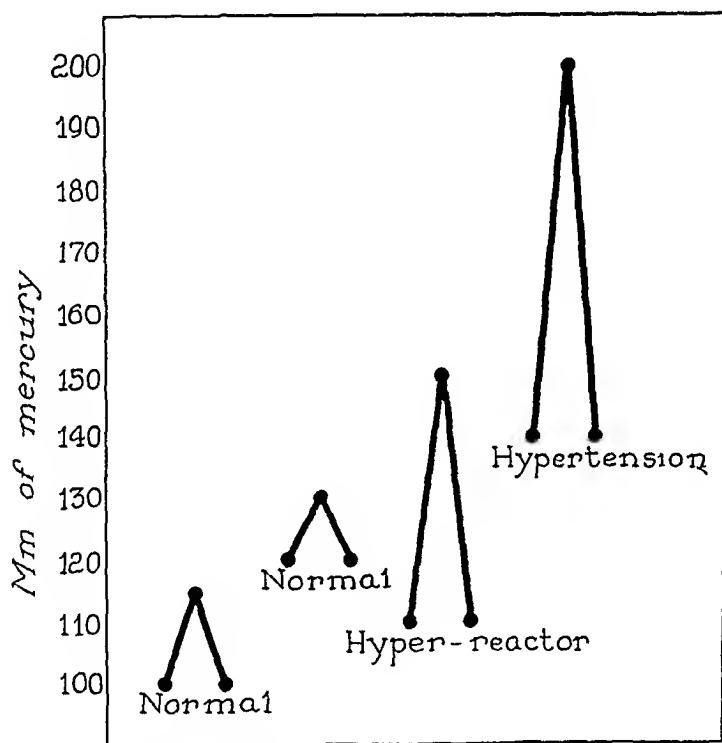


FIG 1 Response of systolic blood pressure to cold pressor test

may be a delay in the return of the blood pressure to the previous level. Sedatives and vasodilating drugs should not have been used by the patient for 24 hours before the test is performed. Observations have shown that the emotional factor does not play an important rôle in the response of the blood pressure to this test*.

The test has been used for five years in studying the reactions of the blood pressure of a large group of patients. It divides all persons into two groups: (1) Those who have minimal or "normal" reactions, and (2) those who have excessive or "abnormal" reactions. When the reactions to

* Unpublished data in thesis, "A Clinical Test of Vasomotor Irritability: Blood Pressure Response to Cold," by Edgar A. Hines, Jr. (1933), on file in The Mayo Foundation, The Mayo Clinic, Rochester, Minnesota.

the test were compared with the effects of environment, it appeared that the test is an index of the way in which a person's blood pressure reacts to environmental stimuli. Almost all persons afflicted with essential hypertension have abnormal or excessive reactions. One group of individuals who do not have hypertension gives excessive reactions to the cold pressor test in both systolic and diastolic blood pressure. These individuals have been called "hyperreacting normals" (figure 1). In a study of 400 school children, 18.7 per cent were found to be hyperreactors to the test.⁸ It is believed that this hyperreacting state of the blood pressure of normal persons represents a prehypertensive stage of essential hypertension and that many of these persons eventually will have essential hypertension. The transition from this hyperreactive state to essential hypertension has been observed among a small number of individuals during the five-year period of observation. Because of these significant observations concerning the cold pressor test, I have used the test in a study of the hereditary factor in vasomotor reactivity and in essential hypertension.

METHOD OF STUDY

The observations have been carried out along three lines: (1) a correlation of the type of reaction to the test and the incidence of hypertensive disease in the family history, (2) a study of the reaction of twins to the test, (3) a study of the reaction of members of hypertensive and nonhypertensive families to the test.

DATA

Correlation of the Type of Reaction and the Family History. A detailed study was made of the incidence of hypertensive cardiovascular disease among relatives of 492 "normal reactors" and 116 "hyperreactors." The results were compared with the family history of hypertensive cardiovascular disease in a group of 267 cases of essential hypertension. The results are shown in table I. From this table, it may be seen that a positive

TABLE I
Incidence of Hereditary Factor Among Hypo- and Hyperreactors and Patients with Essential Hypertension

	Number	Family history of hypertensive cardiovascular disease, per cent
Subjects with a normal blood pressure		
Hyporeactors	492	17.2
Hyperreactors	116	84.2
Subjects with essential hypertension	267	86.6

family history of hypertensive cardiovascular disease is five times more frequent among hyperreacting normals than it is among persons who have a

normal blood pressure and give a normal reaction to the cold pressor test. Also, there is a close correlation between the incidence of an hypertensive cardiovascular family history among patients who have essential hypertension and persons who belong in the hyperreacting normal group.

The Blood Pressure Reaction of Twins Seven sets of identical twins and three sets of fraternal twins have been tested. In all of the sets of identical twins the response of one twin to the cold pressor test was similar to that of the other twin, whereas, in two of three sets of fraternal twins, the response was different (figure 2). One of the sets of identical twins

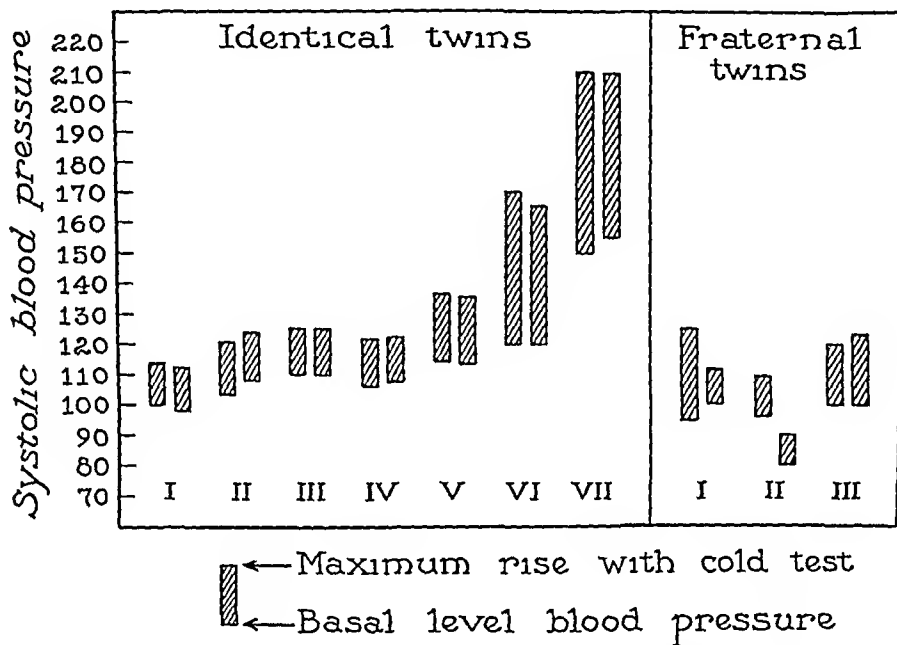


FIG 2 Response of the blood pressure of twins to the cold pressor test

had essential hypertension. Their basal blood pressure readings and response to the test were almost identical.

The Reaction of the Blood Pressure and Presence of Hypertension Among the Members of Hypertensive and Nonhypertensive Families Thirty families, consisting of 256 members, are included in this group. In 12 of these families there was no evidence or history of hypertensive cardiovascular disease, in 18 families there was a definite hypertensive diathesis. Blood pressure readings were made and a cold pressor test was performed on every available living member of each family and a careful inquiry was made as to the cause of death of deceased near relatives. The pedigrees of some of these families are shown in figures 3, 4, 5, and 6. In the family group shown in figure 6, I was able to make blood pressure readings and make the test on every living member of the group, which consisted of 57 members, or three generations.

C-Family (No hypertension)

E-Family (No hypertension)

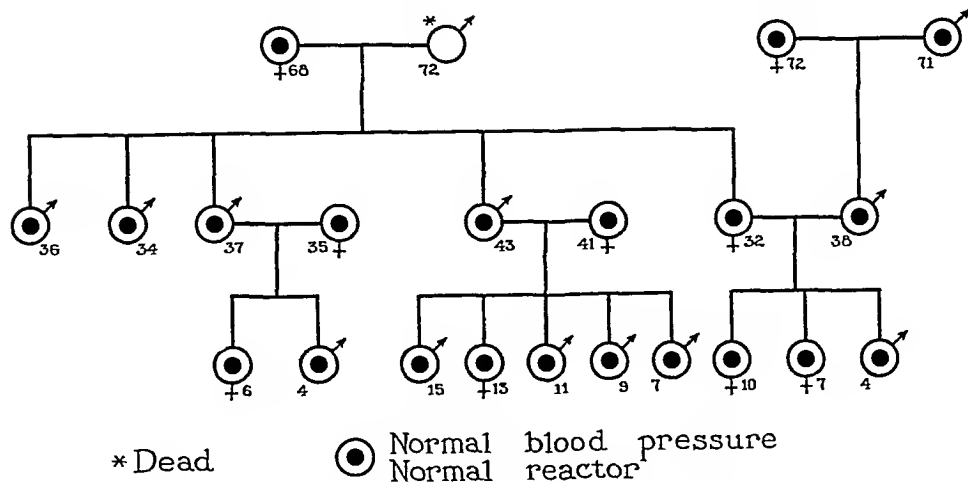


FIG 3 Family tree showing blood pressure and response of blood pressure to cold test in nonhypertensive families

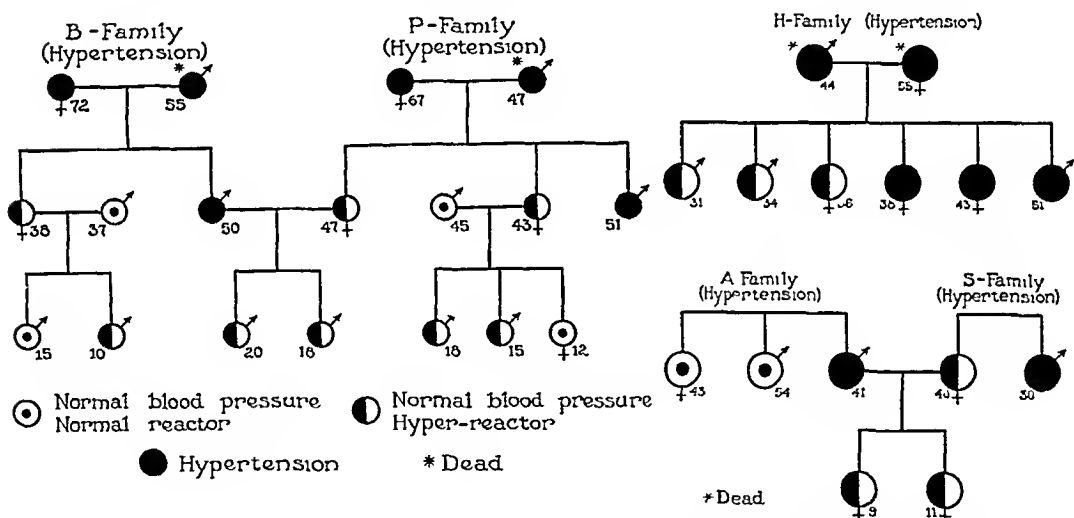


FIG 4 Family trees showing blood pressure and response of blood pressure to cold pressor test in hypertensive families

C Family (Hypertension)

D Family (Hypertension)

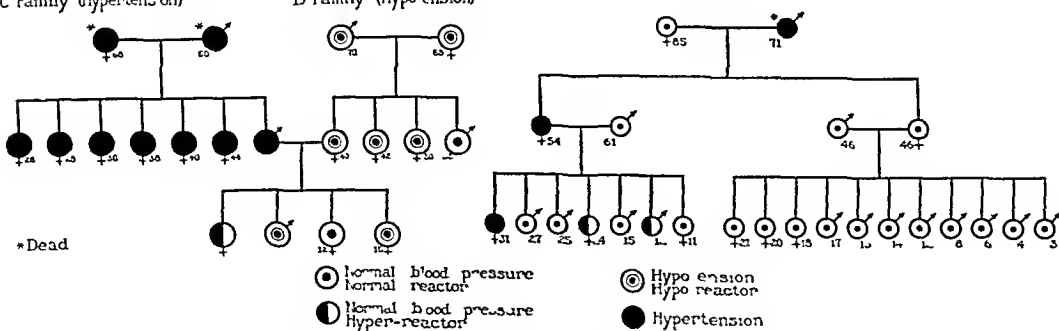


FIG 5 Family trees showing blood pressure and response of blood pressure to cold pressor test in hypertensive and nonhypertensive families and in a family in which hypotension was present

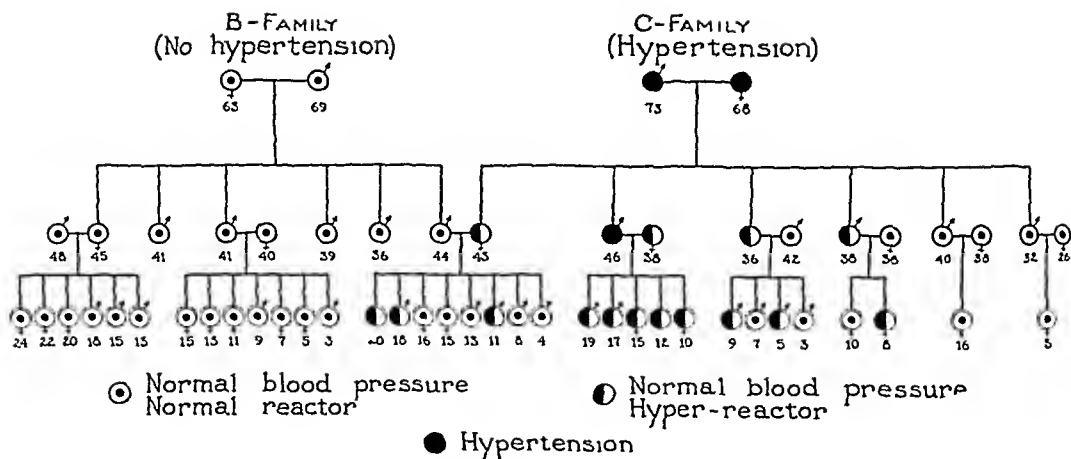


FIG. 6 Family tree showing blood pressure and response of blood pressure to cold pressor test in hypertensive and a nonhypertensive family

Investigation of these data revealed that when both parents had a normal blood pressure and were normal reactors, all of the children were normal reactors. If both parents had hypertension or were hyperreacting normals, 95 per cent of the children had hypertension or were hyperreactors to the test, and if one parent had hypertension or was a hyperreactor and the other parent was a normal reactor, 43.4 per cent of the children were hyperreactors or had hypertension. In three families of two generations, the parents had essential hypertension or had died of it and all of the children had hypertension or were hyperreactors.

SUMMARY AND CONCLUSIONS

The hereditary factor in essential hypertension has been considered. Data have been presented regarding the reaction of the blood pressure to a standard stimulus (cold pressor test) in 608 cases in which the blood pressure was "normal," in 10 pairs of twins, and in 256 members of 30 hypertensive and nonhypertensive families. A study has also been made of the family history of the 608 individuals who had a normal blood pressure and of 267 individuals who had essential hypertension. A positive family history of hypertensive cardiovascular disease is five times as frequent among individuals who have hypertension or who are hyperreactors to a standard stimulus test than it is among individuals who react normally to the test. In the study of the twins and the family groups it was found that the type of blood pressure reaction to the test followed an inherited pattern. Inasmuch as I so far have not found any hyperreactor who did not have one parent who had hypertension or was a hyperreactor, it is probable that the trait is inherited as a dominant characteristic. The excessive or "hypertensive" type of reaction occurred predominantly among members of families in which there was an hypertensive diathesis. These findings are considered

to be strong evidence that the hereditary factor plays an important rôle in the development of essential hypertension. The inherited quality may be a vasomotor system which reacts excessively to certain external and internal stimuli and eventually results in the development of essential hypertension in many cases.

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FACTORS INFLUENCING THE PROGNOSIS IN DIABETIC COMA^{*}

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IN making this report we have two purposes, first to present briefly chemical and clinical data of cases of diabetic acidosis as encountered in a large city hospital, and second to evaluate data determined at admission in regard to their effect on the prognosis.

For many years we have been impressed with the fact that both the rate of incidence and the mortality rate of acidosis are much higher in diabetics of the economic and intellectual class of society which is dependent on the city hospital than in those diabetics seen in private practice. During the six years 1931 to 1936 there were admitted to the wards of the Metabolic Division, Philadelphia General Hospital, 3009 cases of diabetes, 268 of these patients were admitted in acidosis and it is their records which form the material of this report. There were 224 individuals, as 21 patients were admitted in acidosis 44 additional times. Eleven patients were admitted in acidosis twice, four patients three times, four patients four times, one patient five times, and one patient ten times. The latter patient (No. 252) was given a job in the hospital nearly two years ago and has not been in coma during this time.

The Metabolic Division has its own trained personnel and physical equipment, consisting of two wards of 25 beds each, laboratories, diet kitchen and out-patient department, all located as a single unit. All the diabetics of the hospital are concentrated in this department regardless of complications, except cases of open tuberculosis and psychopathic patients. Without this department the diabetic patients would be scattered among ten medical services, four surgical services and numerous special services. The out-patients consist only of patients who have been discharged from the wards. As a result of the above circumstances a new patient usually is one who has come to the hospital only because of some serious complaint or complication, and who knows little or nothing about diabetes, and about whom the staff has no information. Of the 224 individual patients in this report, 82 patients did not know they had diabetes at the onset of the acidosis which caused them to be admitted to the hospital.

In a large series of uncontrolled diabetics, all degrees of acidosis occur and it is difficult to decide which cases are worthy to be included in a report. Some authors give no criteria concerning the basis of selection of the cases included in their reports. More usually the authors have selected some figure for the CO_2 volume per cent and included all cases below that figure.

^{*} Presented at the St. Louis meeting of the American College of Physicians, April 22, 1937.

The figures selected have varied widely, ranging from 15¹ to 45² Joslin³ in his seven reports has included cases of 20 and below In this report all cases have been reported in which the CO₂ volume per cent was 29 or lower The reasons for selecting this figure will be discussed later in this report

Of the 268 cases admitted in acidosis 117 died, a mortality of 43.7 per cent Some years ago, when it became obvious to us that our mortality was much larger than that reported from other clinics, we made a careful study of our records for the purpose of analyzing the causes of the high mortality and with the hope of reducing it Because of the large number of patients having serious complications, we found it necessary to separate the cases into groups and the criteria which we set up were as stated in table 1

TABLE I

Criteria Used to Group the Diseases Complicating Diabetic Acidosis

- A No complicating disease (cases recovering = AR, cases dying = AD)
- B 1 Any disease sufficient to precipitate coma in a diabetic, but not severe enough to cause death as a rule in a non-diabetic
- 2 Any disease severe enough to cause considerable mortality in non-diabetics If the case of acidosis dies, he has been out of acidosis less than 48 hours prior to death (cases recovering = BR, cases dying = BD)
- C 1 Like B₂, except that all cases die, but have been out of acidosis more than 48 hours prior to death
- 2 Any disease the mortality of which would be very high in non-diabetics in a short period of time The acidosis is merely a terminal event of the fatal disease
- 3 Any disease from which the patient dies many days after complete recovery from the acidosis

It will be noted that the certainty of a patient's having died from the complication and not the acidosis increases progressively from B₁ to C₃ in this table In general the "A" cases had no complications, the "B" cases had complications but when death occurred the chief factor was probably the acidosis, and the "C" cases all died, the complications being of such severity that all would probably have died even if there had been no acidosis

We have included as complications only such conditions as were likely to precipitate acidosis General conditions such as arteriosclerosis, latent syphilis, etc., are not included regardless of what effect they may have had on the general vitality of the patient We have not regarded anuria as a complication, but as a condition directly dependent upon the acidosis

There were 129 uncomplicated cases and 139 cases with complications In the "A" group (tables 2 and 3) 97 recovered and 32 died, the mortality being 24.8 per cent In the "B" group (tables 4 and 5) 54 recovered and 27 died, the mortality being 33.3 per cent In the "C" group (table 6) all 58 cases died, of which, however, 19 cases died many days after recovery from the acidosis In tables 7 to 15 the letters "AR" refer to cases recovering in the "A" group, "AD" to cases dying in the "A" group, "BR" to cases recovering in the "B" group, "BD" to cases dying in the "B" group, "C₁C₂" and "C₃" to cases as set forth in table 1, "R" to total cases recovering and "D" to total cases dying, following which the mortal-

TABLE II
PHILADELPHIA GENERAL HOSPITAL
Diabetic Acidosis with No Complications Cases Recovering (AR)

	Patient No	Age	Sex	Color	Date Admitted	Blood Findings on Admission				On Admission		
						Sugar mg %	CO ₂ vol %	Urea N mg %	W B C thous	Men- tally	Dura- tion Aci- dosis	Known Dia- betic
1	12	21	F	B	1/ 6/31	348	24	13	9 7	C	3	Yes
2	120	16	F	W	4/10/31	328	14	16	14 0	U	4	No
3	124	29	F	W	4/14/31	576	21	18	—	C	—	Yes
4	132	8	F	W	4/18/31	400	18	12	18 9	C	1	Yes
5	12	22	F	B	4/21/31	350	22	13	10 4	C	2	Yes
6	165	48	F	B	5/20/31	568	12	34	22 9	C	—	No
7	12	22	F	B	6/11/31	348	25	10	—	C	3	Yes
8	211	19	F	B	7/20/31	480	13	9	21 7	C	3	Yes
9	254	26	M	B	8/27/31	410	21	10	5 5	C	—	Yes
10	254	26	M	B	12/ 2/31	348	20	15	—	C	2	Yes
11	348	30	M	B	12/24/31	720	24	65	—	C	—	No
12	368	15	F	W	1/ 6/32	320	27	11	—	C	2	Yes
13	408	21	F	W	2/15/32	464	14	18	21 5	C	—	—
14	415	11	M	B	2/23/32	304	20	18	—	C	3	No
15	427	26	F	W	3/17/32	608	14	17	29 4	U	—	No
16	492	13	M	W	5/14/32	344	17	10	—	C	—	Yes
17	252	17	M	B	5/10/32	280	20	14	21 6	C	2	Yes
18	79	23	M	W	7/13/32	364	22	11	5 6	C	4	Yes
19	132	9	F	W	7/17/32	480	18	14	20 4	C	3	Yes
20	132	9	F	W	7/27/32	324	22	12	4 4	C	1	Yes
21	588	24	F	W	9/ 9/32	340	24	14	—	C	3	Yes
22	590	10	F	W	9/10/32	280	20	10	—	C	3	Yes
23	120	18	F	W	9/28/32	320	17	11	17 6	C	1	Yes
24	252	17	M	B	10/ 4/32	400	21	22	14 0	C	—	Yes
25	390	28	M	W	10/11/32	388	17	12	42 6	C	2	Yes
26	415	12	M	B	11/ 4/32	290	23	12	—	C	—	Yes
27	658	20	F	W	11/12/32	462	16	20	29 5	C	3	Yes
28	688	25	M	B	12/14/32	290	13	12	—	C	4	Yes
29	252	17	M	B	1/ 5/33	556	11	21	13 8	C	4	Yes
30	716	52	F	W	1/10/33	286	26	13	—	C	—	Yes
31	723	38	F	W	1/18/33	236	23	26	—	C	2	—
32	739	38	F	W	1/28/33	434	27	27	—	C	1	Yes
33	252	17	M	B	2/ 6/33	396	19	18	24 8	C	—	Yes
34	658	21	F	W	3/15/33	610	14	15	—	U	2	Yes
35	120	18	F	W	3/20/33	316	20	11	14 5	C	1	Yes
36	20	11	M	W	4/ 2/33	337	15	11	—	C	1	Yes
37	890	29	F	B	6/11/33	414	16	15	—	C	4	Yes
38	861	23	M	W	7/ 5/33	720	18	19	17 0	C	3	Yes
39	423	28	F	W	7/ 9/33	448	17	14	19 8	C	—	Yes
40	946	43	F	B	8/ 6/33	580	12	30	23 5	U	4	Yes
41	963	48	F	B	8/23/33	384	24	24	—	C	—	Yes
42	977	52	F	W	9/10/33	464	18	41	—	C	2	Yes
43	252	18	M	B	10/ 2/33	655	22	18	23 5	C	2	Yes
44	1038	38	F	B	11/ 7/33	806	16	28	18 8	U	4	Yes
45	897	28	F	B	1/12/34	150	19	12	—	C	3	Yes
46	1128	16	F	W	3/ 7/34	346	25	9	9 8	C	—	Yes
47	1253	54	F	W	6/28/34	624	27	18	—	C	—	No

TABLE II—*Continued*

	Patient No	Age	Sex	Color	Date Admitted	Blood Findings on Admission				On Admission		
						Sugar mg %	CO ₂ vol %	Urea N mg %	W B C thous	Men- tally	Dura- tion Acidosis	Known Dia- betic
48	252	19	M	B	7/ 4/34	464	10	16	—	C	3	Yes
49	252	19	M	B	9/10/34	388	16	17	13 2	C	4	Yes
50	415	13	M	B	9/10/34	300	26	13	14 3	C	1	Yes
51	128	20	M	W	9/20/34	468	23	21	28 4	C	2	Yes
52	1128	16	F	W	10/ 8/34	320	11	12	22 6	C	4	Yes
53	178	18	F	W	10/18/34	400	24	12	—	C	3	Yes
54	875	39	M	B	10/31/34	324	27	11	10 6	C	3	Yes
55	1396	11	F	B	11/30/34	352	20	14	20 3	C	4	Yes
56	1404	57	M	W	12/10/34	756	13	12	48 3	C	1	Yes
57	848	20	M	W	1/ 6/35	904	15	30	17 5	C	3	Yes
58	1440	39	F	B	1/20/35	1024	15	63	19 3	U	1	No
59	1450	16	F	B	1/30/35	680	13	19	20 3	U	3	No
60	1463	38	F	B	2/ 5/35	708	12	15	20 0	C	1	No
61	252	20	M	B	2/27/35	808	12	30	54 7	C	2	Yes
62	1511	22	M	B	3/20/35	1056	14	43	27 5	C	4	No
63	1519	42	F	W	3/29/35	612	12	35	41 5	U	3	Yes
64	252	20	M	B	5/ 6/35	800	14	35	36 9	C	3	Yes
65	1608	42	F	B	6/18/35	992	19	38	17 8	C	4	No
66	1450	16	F	B	6/25/35	480	16	10	23 1	C	3	Yes
67	1671	16	F	W	8/21/35	296	22	23	7 9	C	—	No
68	1685	48	F	B	9/ 6/35	848	11	21	24 2	C	2	No
69	1450	16	F	B	9/ 6/35	352	14	11	18 5	C	4	Yes
70	1543	46	F	W	9/ 9/35	912	11	34	21 5	C	3	Yes
71	1474	13	F	W	10/15/35	374	14	15	25 3	C	—	Yes
72	1748	21	F	W	11/ 2/35	320	18	16	12 6	C	4	No
73	1788	51	F	W	12/ 8/35	600	13	22	45 9	U	2	Yes
74	1808	52	M	W	1/ 3/36	600	22	65	11 0	C	4	Yes
75	1689	42	F	W	1/11/36	560	25	16	12 5	C	1	Yes
76	307	59	F	W	1/12/36	1080	15	75	17 0	C	1	Yes
77	1820	52	F	W	1/21/36	262	25	18	—	C	4	No
78	848	22	M	W	2/ 7/36	680	25	28	23 5	C	4	Yes
79	1193	23	F	W	2/18/36	384	24	13	—	C	—	Yes
80	1474	13	F	W	3/13/36	368	17	12	—	C	—	Yes
81	1881	43	F	W	4/ 4/36	732	13	30	19 3	U	2	Yes
82	1882	60	F	W	4/ 4/36	300	23	17	—	C	2	Yes
83	1827	14	F	W	4/ 4/36	608	14	16	72 1	C	—	Yes
84	1474	13	F	W	4/18/36	464	22	21	32 2	C	1	Yes
85	1936	73	F	B	6/ 8/36	372	29	21	11 0	C	1	Yes
86	964	45	F	B	6/11/36	204	25	10	—	C	4	Yes
87	614	45	M	W	8/ 8/36	1168	17	55	15 1	C	—	Yes
88	1827	14	F	W	8/31/36	296	19	14	18 0	C	—	Yes
89	2001	39	M	B	9/ 2/36	415	25	45	—	C	2	Yes
90	2032	12	M	W	9/30/36	800	19	27	51 0	C	1	Yes
91	2036	32	M	B	10/ 2/36	440	18	14	—	C	3	Yes
92	1827	14	F	W	10/14/36	366	26	13	22 6	C	—	Yes
93	807	40	F	W	10/31/36	270	14	17	11 5	C	3	Yes
94	1827	14	F	W	12/10/36	366	23	15	27 5	C	—	Yes
95	193	15	M	W	12/12/36	310	14	10	25 5	C	2	Yes
96	2096	22	M	W	12/22/36	300	25	14	11 5	C	4	Yes
97	72	14	F	W	12/31/36	484	9	16	42 6	C	2	Yes

TABLE III
PHILADELPHIA GENERAL HOSPITAL
Diabetic Acidosis with No Complications Cases Dying (AD)

	Patient No	Age	Sex	Color	Date Admitted	Blood Findings on Admission				On Admission			Post Mortem	Time Lived
						Sugar mg %	CO ₂ vol %	Urea N mg %	W B C thous	Mentally	Duration Acidosis	Known Diabetic		
1	14	52	F	W	1/10/31	404	12	70	22 1	C	3	Yes	p m	9 hrs
2	106	56	F	W	3/26/31	600	22	53	8 7	C	3	Yes	—	6 hrs
3	145	37	F	W	4/14/31	576	15	20	16 8	U	1	No	p m	12 hrs
4	32	16	F	W	3/21/32	728	14	18	45 5	U	2	Yes	—	9 hrs
5	535	35	F	B	7/ 5/32	752	19	60	—	U	3	No	p m	6 hrs
6	186	15	F	W	8/12/32	424	12	10	—	U	3	Yes	—	11 hrs
7	589	65	F	W	9/10/32	960	15	75	20 9	U	4	Yes	—	11 hrs
8	666	22	F	B	11/23/32	450	18	22	10 5	U	4	No	—	12 hrs
9	973	45	M	W	9/ 6/33	728	12	23	14 5	U	1	Yes	p m	24 hrs
10	988	25	F	W	9/21/33	770	14	30	29 8	U	3	Yes	p m	14 hrs
11	1006	56	F	W	10/ 7/33	808	21	—	—	U	3	Yes	—	3 hrs
12	1113	50	F	B	2/14/34	740	23	90	5 8	—	—	No	p m	15 hrs
13	1173	21	F	W	4/17/34	368	12	22	—	U	4	No	p m	18 hrs
14	1227	53	F	B	6/10/34	1028	12	—	—	U	3	No	—	3 hrs
15	1250	30	M	B	6/26/34	770	17	—	—	C	4	No	—	7 hrs
16	1267	30	M	W	7/17/34	428	11	—	—	U	3	No	p m	7 hrs
17	1295	35	F	W	8/10/34	720	13	40	—	U	4	Yes	p m	10 hrs
18	1296	51	F	W	8/12/34	386	14	14	22 4	C	4	No	—	15 hrs
19	1325	38	M	B	9/18/34	682	10	65	15 3	U	4	No	p m	3 hrs
20	86	40	F	W	10/ 9/34	1000	7	20	31 6	U	2	Yes	—	16 hrs
21	1347	52	F	W	10/15/34	568	26	57	24 9	U	4	Yes	—	4 hrs
22	1439	25	F	W	1/19/35	370	28	27	6 1	C	2	No	—	8 hrs
23	1566	46	M	W	5/ 8/35	200	27	43	12 6	U	3	Yes	p m	26 hrs
24	1576	36	M	B	5/16/35	1256	18	78	11 8	U	2	No	p m	2 hrs
25	1594	12	M	W	5/31/35	960	14	22	23 4	U	1	No	p m	21 days
26	1706	50	F	W	9/29/35	500	14	34	10 6	U	3	No	p m	7 hrs
27	1555	57	M	W	2/ 6/36	1000	14	20	25 5	U	4	Yes	p m	20 hrs
28	1955	60	F	B	6/27/36	880	14	57	18 4	U	4	No	—	19 hrs
29	2035	65	F	B	10/ 1/36	520	13	60	24 9	U	4	Yes	p m	18 hrs
30	2081	52	F	B	12/ 5/36	720	13	55	39 5	U	—	Yes	p m	32 hrs
31	2089	52	M	W	12/15/36	1528	25	113	14 7	U	—	No	—	6 hrs
32	2100	59	F	W	12/26/36	1008	12	55	34 8	U	3	Yes	—	5 hrs

ity is given. Because the 19 "C₃" cases recovered from the acidosis, the mortality has also been calculated with these cases regarded as recoveries instead of deaths, and "R + C₃" refers to total recoveries plus the "C₃" cases, and "D — C₃" refers to total deaths minus the "C₃" cases. If the 19 "C₃" cases are regarded as recoveries, the total mortality for the entire 268 cases becomes 36.6 per cent. In tables 5 and 6 the + and — signs in the "group" column indicate whether the CO₂ was above 40 prior to death.

In the 139 cases with complications there were 105 cases with infections, of which 68 occurred in the "B" group and 37 in the "C" group. The location of the infections was as follows: Respiratory system (except tu-

TABLE IV
PHILADELPHIA GENERAL HOSPITAL
Diabetic Acidosis with Complications Cases Recovering (BR)

Patient No	Age	Sex	Color	Date Admitted	Blood Findings on Admission				On Admission			Group	Complications	
					Sugar mg %	CO vol %	Urea N mg %	W B C thous	Mentally	Duration Acidosis	Known Diabetic			
1	25	19	M	W	1/17/31	325	25	9	16 0	C	—	Yes	B2	Active pulmonary tuberculosis
2	30	63	F	W	1/21/31	218	29	—	11 1	C	—	No	B2	Hyperthyroidism
3	43	27	M	B	1/29/31	330	29	16	18 6	C	—	Yes	B1	Otitis media
4	43	27	M	B	3/16/31	400	25	14	—	C	—	Yes	B2	Mastoiditis
5	181	62	M	B	6/ 6/31	200	24	17	—	U	—	Yes	B2	Frontal lobe tumor—removed
6	185	46	F	B	6/12/31	1056	18	55	27 7	C	4	No	B2	Broncho-pneumonia
7	202	28	F	B	7/10/31	241	14	14	24 2	C	2	Yes	B2	Pulmonary abscess
8	221	46	F	W	7/28/31	284	14	14	15 7	C	2	Yes	B2	Carbuncle of chin
9	287	42	F	B	10/15/31	528	16	35	16 4	U	1	No	B2	Hyperthyroidism
10	317	42	F	B	11/14/31	282	27	24	—	C	3	Yes	B1	Infectious arthritis
11	252	16	M	B	12/18/31	574	17	14	26 4	C	3	Yes	B2	Broncho pneumonia
12	287	42	F	B	1/ 3/32	632	12	24	—	C	4	Yes	B2	Hyperthyroidism
13	418	19	M	W	3/ 1/32	320	28	9	15 2	C	—	Yes	B2	Carbuncle of neck
14	192	18	M	W	3/15/32	416	18	17	10 4	C	3	Yes	B2	Influenzal pneumonia
15	443	39	M	W	3/20/32	662	12	22	31 5	C	4	Yes	B2	Erysipelas of face
16	120	17	F	W	3/23/32	288	17	7	17 6	C	—	Yes	B1	Acute tonsillitis
17	512	17	F	W	6/ 4/32	448	9	12	18 8	C	4	No	B2	Suppurative mastoiditis
18	481	28	F	W	5/ 5/32	540	15	30	—	C	4	Yes	B2	Suppurative parotitis
19	560	35	F	B	8/10/32	338	20	14	—	C	4	No	B1	Ischio rectal abscess
20	287	42	F	B	8/12/32	600	11	27	16 0	C	—	Yes	B2	Hyperthyroidism
21	78	17	M	W	9/29/32	280	16	12	17 9	C	2	Yes	B1	Acute pharyngitis
22	624	72	M	W	10/ 4/32	328	29	15	6 4	C	—	Yes	B2	Gangrene of foot
23	721	57	M	W	1/12/33	262	27	27	—	C	—	Yes	B2	Erysipelas of face and back
24	736	53	M	W	1/27/33	442	20	—	49 5	C	—	—	B2	Abscess of back
25	178	16	F	W	4/21/33	428	29	12	15 8	C	1	Yes	B1	Suppurative endometritis
26	884	40	F	B	6/ 6/33	406	17	22	18 4	C	—	No	B2	Carbuncle of back
27	897	28	F	B	6/14/33	212	15	15	15 4	C	4	No	B1	Acute alcoholism
28	919	57	F	W	7/10/33	224	29	11	—	C	4	No	B1	Infected foot
29	319	15	F	W	9/30/33	380	18	15	21 4	C	1	Yes	B1	Acute enteritis
30	936	55	M	W	10/15/33	178	27	27	13 2	C	1	Yes	B1	Acute alcoholism
31	193	12	M	W	12/18/33	400	15	13	27 8	C	3	Yes	B1	Upper respiratory infection
32	1072	33	M	W	1/ 7/34	536	11	20	23 2	C	3	Yes	B1	Acute enteritis
33	453	16	M	W	9/ 6/34	520	24	47	4 5	C	3	Yes	B1	Ulcerative colitis
34	1333	25	F	B	9/24/34	137	22	12	14 3	C	3	No	B2	Acute cholangitis
35	1409	55	M	W	12/13/34	604	23	65	13 0	U	3	No	B2	Acute parotitis
36	292	60	F	B	12/21/34	466	23	17	—	C	—	Yes	B2	Gangrene—thigh amputation
37	1419	21	F	B	12/23/34	1850	13	95	12 7	C	3	No	B2	Lobar pneumonia
38	1512	31	F	W	3/20/35	548	21	14	22 7	C	2	Yes	B1	Acute bronchitis
39	1583	24	M	W	5/24/35	816	14	48	45 5	U	2	No	B1	Acute pharyngitis
40	1128	17	F	W	5/29/35	232	29	15	—	C	—	Yes	B1	Upper respiratory infection
41	1599	43	F	B	6/ 5/35	300	16	16	22 4	C	2	No	B2	Carbuncle of neck
42	415	14	M	B	8/18/35	324	24	20	15 7	C	1	Yes	B1	Upper respiratory infection
43	277	35	F	W	8/26/35	864	20	17	57 1	C	1	Yes	B1	Acute enteritis
44	1583	24	M	W	9/25/35	428	25	17	16 6	C	3	Yes	B1	Acute alcoholism
45	1757	58	F	B	11/12/35	345	20	16	14 6	C	3	Yes	B1	Fracture of ankle
46	1772	44	M	B	11/22/35	310	29	18	12 8	C	3	Yes	B2	Prostatic abscess
47	1474	13	F	W	12/18/35	300	23	16	12 8	C	1	Yes	B1	Upper respiratory infection
48	1846	39	M	W	3/ 1/36	380	28	14	30 6	C	4	No	B1	Cellulitis of leg
49	1614	45	M	W	4/29/36	1360	12	40	54 5	C	3	Yes	B1	Acute alcoholism
50	1474	14	F	W	6/16/36	640	13	18	29 3	C	1	Yes	B2	Empyema
51	1967	46	F	W	7/14/36	400	16	18	25 3	C	3	No	B2	Infected foot—thigh amputation
52	1974	50	F	W	7/25/36	560	27	24	—	C	—	No	B2	Gangrene—thigh amputation
53	2063	43	F	W	11/10/36	320	28	9	—	C	—	Yes	B2	Active pulmonary tuberculosis
54	1450	18	F	B	11/26/36	420	6	16	30 0	C	3	Yes	B1	Abscess of thigh

berculosis) 36, gastrointestinal system 14, genito-urinary 9, skin and subcutaneous tissues 16, feet 16, miscellaneous 5, pulmonary tuberculosis 9. Of the 34 non-infections, 13 were in the "B" group and 21 in the "C" group. These consisted of coronary occlusion 7, hyperthyroidism 6, acute alcoholism 4, cancer 3, apoplexy 2, hypertensive congestive failure 2 and miscellaneous 10.

Of the 117 cases which died, postmortem examinations were made in 68 cases, 58.1 per cent of the deaths. Postmortem examinations are indispensable for making accurate final diagnoses in cases dying in diabetic acidosis. When patients in acidosis are admitted with inadequate histories or no histories at all, and die without coming out of acidosis, the presence of complications, their nature and severity often can only be guessed at, and not infrequently they are missed entirely unless postmortem examinations are made. Recent examples of cases in which the complication was not diagnosed during life are patients 1985 (C 36), 1999 (C 37) and 2076 (C

TABLE V
PHILADELPHIA GENERAL HOSPITAL
Diabetic Acidosis with Complications Cases Dying (BD)

	Patient No	Age	Sex	Color	Date Admitted	Blood Findings on Admission				On Admission			Group	Complications	Post mortem	Time Lived
						Sugar mg %	CO vol %	Urea N mg %	WBC thous	Mentally	Duration Acidosis	Known Diabetic				
1	309	64	M	W	11/ 9/31	298	24	110	4.0	C	4	No	B2+	Empyema of gall bladder	—	24 hrs
2	399	4	M	W	2/ 7/32	440	14	—	43.5	O	1	Yes	B1-	Pertussis	p m	7 hrs
3	452	47	F	B	4/12/32	900	23	48	18.3	U	3	No	B2+	Lobar pneumonia	—	26 hrs
4	561	55	F	W	8/12/32	400	10	28	—	U	3	Yes	B2-	Erysipelas	—	18 hrs
5	603	38	F	B	9/20/32	460	15	16	—	U	2	Yes	B1+	Abscess of Bartholin's gland	p m	12 hrs
6	631	39	M	B	10/13/32	500	27	53	—	U	4	No	B2+	Portal cirrhosis pneumonia	p m	12 hrs
7	636	62	F	B	10/19/32	300	9	25	—	U	4	Yes	B2-	Septicemia	—	11 hrs
8	287	43	F	B	12/ 6/32	640	16	55	73.2	U	—	Yes	B2+	Hyperthyroidism	p m	22 hrs
9	750	61	F	W	2/10/33	486	24	26	—	U	2	No	B2-	Resolving pneumonia	—	2 hrs
10	906	66	F	W	6/24/33	440	19	30	—	U	—	No	B2-	Acute pleurisy	—	9 hrs
11	1067	57	F	W	1/ 2/34	380	13	23	18.6	U	4	Yes	B2-	Coronary occlusion	p m	11 hrs
12	360	22	M	W	2/21/34	464	14	—	—	C	3	Yes	B2+	Abscess of jaw	—	5 hrs
13	1164	62	F	W	4/ 8/34	456	24	49	—	U	1	Yes	B2-	Active pulmonary tuberculosis	p m	12 hrs
14	1196	48	F	B	5/ 9/34	480	21	40	—	U	—	No	B2+	Tuberculous pneumonia	—	10 hrs
15	1198	56	F	B	5/10/34	620	15	97	—	C	2	Yes	B2+	Gangrene of foot	—	14 hrs
16	1211	42	F	W	5/24/34	402	16	36	—	U	3	Yes	B2-	Erysipelas of face	—	8 hrs
17	1268	33	F	B	7/ 7/34	370	22	21	14.2	C	4	No	B2+	" " "	—	18 hrs
18	1272	34	F	B	7/21/34	736	18	—	—	U	4	No	B2-	" " "	—	9 hrs
19	1342	54	F	B	10/ 5/34	1008	22	95	25.8	U	3	No	B2+	" " "	p m	50 hrs
20	1402	61	F	W	12/ 4/34	370	19	15	15.9	C	4	Yes	B2+	Broncho pneumonia	p m	49 hrs
21	1415	56	F	W	12/18/34	412	15	26	16.5	C	4	No	B2-	Broncho pneumonia	—	12 hrs
22	1483	56	F	W	2/28/35	1470	10	42	25.0	U	3	Yes	B2-	Gangrene of both feet	p m	2 hrs
23	1760	48	F	B	11/13/35	540	10	56	14.1	U	4	No	B1+	Bilateral parotitis	p m	5 days
24	1840	48	F	B	2/20/36	1290	16	60	24.0	U	4	No	B2+	Gangrenous cecum peritonitis	p m	39 hrs
25	1376	65	F	W	7/11/36	400	13	26	—	U	4	Yes	B2-	Fractured ribs hemothorax	p m	1 hr
26	1545	65	F	W	9/19/36	440	24	52	12.8	C	4	Yes	B2-	Pyelonephritis	—	18 hrs
27	2073	51	F	W	11/21/36	240	27	11	16.6	C	4	Yes	B2+	Carbuncle of neck pneumonia	p m	3 days

39) The first case was a colored woman aged 49, admitted 8/5/36. She was not known to be diabetic. Her sister stated that she had been working until three days prior to admission and for three days had been extremely weak. She was unconscious at admission and died in 31 hours. At autopsy miliary tuberculosis was found. The second case was a colored woman aged 76, admitted 8/27/36. A friend stated she had been well until seven days prior to admission, since when she had been weak and compelled to stay in bed. Her friend knew she was a large water drinker but did not know whether she had diabetes. Her urine contained large numbers of leukocytes. She was unconscious at admission and died in 17 hours. At autopsy multiple abscesses of the kidneys were found. The third case was

TABLE VI
PHILADELPHIA GENERAL HOSPITAL
Diabetic Acidosis Cases Dying from Complications (C)

	Patient No	Age	Sex	Color	Date Admitted	Blood Findings on Admission				On Admission			Group	Complications	Post mortem	Time Lived
						Sugar mg %	CO ₂ vol %	Urea N mg %	WBC thous	Mentally	Duration Acidosis	Known Diabetic				
1	34	14	F	W	3/ 8/31	278	14	14	24.5	C	4	Yes	C1+	Influenza	p m	4 days
2	253	60	M	W	8/25/31	202	28	28	33.6	C	—	—	C2-	Coronary occlusion	—	17 hrs
3	279	19	F	W	10/ 1/31	656	18	22	25.8	U	3	No	C1+	Ruptured appendix peritonitis	—	4 days
4	295	63	F	W	10/24/31	456	29	45	15.0	U	4	Yes	C2+	Coronary occlusion	—	24 hrs
5	306	45	M	W	11/ 5/31	290	22	10	—	C	4	No	C2+	Lobar pneumonia	—	7 days
6	349	60	F	W	12/27/31	512	14	40	—	C	4	Yes	C1+	Lobar pneumonia with abscess	p m	20 hrs
7	586	55	M	W	9/ 8/32	480	11	21	24.0	C	1	Yes	C2-	Gangrene of foot	p m	7 hrs
8	611	49	F	W	9/24/32	532	17	16	19.9	C	3	Yes	C2-	Active pulmonary tuberculosis	—	13 hrs
9	639	54	M	W	10/21/32	372	26	14	36.6	C	3	Yes	C2+	Septicemia staphylococcus aureus	p m	48 hrs
10	655	57	M	W	11/ 9/32	414	27	26	35.4	C	3	No	C2+	Carbuncle of neck	—	14 hrs
11	714	42	F	W	1/ 8/33	468	18	10	—	C	—	—	C1+	Lobar pneumonia	—	6 days
12	715	50	F	W	1/ 9/33	536	25	14	14.5	C	2	Yes	C2+	Cerebral thrombosis	—	24 hrs
13	732	46	F	B	1/24/33	486	15	63	7.5	C	3	No	C2-	Acute hemorrhagic pancreatitis	p m	16 hrs
14	759	74	F	W	2/16/33	588	17	—	17.6	U	3	Yes	C2-	Gangrene of foot abscess of back	p m	12 hrs
15	765	50	F	B	2/22/33	640	13	50	15.5	U	2	No	C2-	Acute hemorrhagic pancreatitis	p m	22 hrs
16	768	52	F	W	2/26/33	486	28	22	—	U	1	—	C2+	Cerebral thrombosis	p m	15 hrs
17	205	74	M	W	8/10/33	96	26	20	—	U	2	Yes	C2-	Abdominal carcinomatosis	p m	8 hrs
18	1021	65	F	W	10/ 8/33	202	13	—	4.0	U	4	—	C2-	Fernicious aemia (?)	—	7 hrs
19	427	27	F	W	1/ 1/34	636	22	28	—	C	4	Yes	C2-	Carbuncle of chin abscess of kidney	—	27 hrs
20	785	58	F	W	1/20/34	496	23	38	45.3	C	4	Yes	C1+	Brocho pneumonia	—	3 days
21	1092	43	F	B	1/26/34	592	19	15	24.3	C	4	No	C2+	Coronary occlusion	p m	2 days
22	1143	29	F	B	3/20/34	504	18	12	13.0	U	3	Yes	C2-	Peritonitis	—	17 hrs
23	1146	46	F	B	3/22/34	508	13	16	14.5	U	4	No	C2+	Tuberculous pneumonia	p m	18 hrs
24	1151	40	F	B	3/24/34	608	15	29	22.3	C	4	No	C2+	Gangrene of both feet	p m	16 hrs
25	1183	60	F	W	4/27/34	640	14	—	23.1	C	1	No	C2-	Carcinoma of cervix	—	12 hrs
26	1411	73	F	W	12/14/34	400	15	16	9.5	C	3	No	C2+	Broncho pneumonia septicemia	—	16 hrs
27	1467	55	F	W	2/12/35	280	23	125	50.9	C	3	Yes	C2-	Coronary occlusion	—	16 hrs
28	1592	72	F	W	5/30/35	320	24	17	28.0	C	—	Yes	C2+	Gangrene—thigh amputation	p m	57 hrs
29	1595	48	F	W	6/ 1/35	704	26	52	11.9	U	—	No	C2-	Chronic pancreatitis with stone	p m	7 hrs
30	616	60	M	W	7/25/35	280	12	165	26.1	U	—	Yes	C2-	Chronic pancreatitis with stone	p m	4 hrs
31	1649	83	F	B	8/ 4/35	896	18	53	14.5	U	2	Yes	C2+	Chronic pancreatitis with stone	p m	11 hrs
32	1707	44	F	B	9/29/35	290	10	15	40.9	U	4	Yes	C2+	Chronic pancreatitis with stone	p m	34 hrs
33	1732	40	F	B	10/20/35	568	22	40	—	U	—	No	C2-	Chronic pancreatitis with stone	p m	2 hrs
34	1783	62	F	W	12/ 3/35	456	21	29	21.0	C	3	Yes	C2+	Chronic pancreatitis with stone	p m	20 hrs
35	1838	40	F	B	2/17/36	800	12	60	16.4	U	4	No	C1+	Broncho pneumonia	p m	8 days
36	1985	49	F	B	3/ 5/36	874	10	46	12.1	U	3	No	C2+	Miliary tuberculosis	p m	31 hrs
37	1999	76	F	B	8/27/36	680	12	60	29.7	U	4	—	C2+	Abscesses of kidneys	p m	17 hrs
38	1270	64	F	W	9/16/36	490	23	38	—	C	4	Yes	C2-	Coronary occlusion	p m	14 hrs
39	2076	55	F	W	11/26/36	310	14	21	19.5	C	4	No	C2-	Ruptured appendix peritonitis	p m	14 hrs
40	160	60	F	B	5/15/31	976	24	63	16.8	C	2	No	C3+	Gangrene of foot	p m	10 days
41	248	20	F	B	8/21/31	268	29	11	—	C	3	Yes	C3+	Active pulmonary tuberculosis	—	35 days
42	286	40	F	B	10/24/31	488	26	65	—	C	3	No	C3+	Chronic nephritis	p m	9 days
43	459	45	F	B	4/18/32	480	26	90	29.9	C	—	Yes	C3+	Subacute nephritis	p m	8 days
44	704	52	F	B	1/ 6/33	640	18	52	7.8	C	1	No	C3+	Abscesses of kidneys	p m	6 days
45	872	73	F	B	5/24/33	350	29	25	18.4	C	4	Yes	C3+	Bilateral suppurative pyelonephritis	p m	13 days
46	924	52	F	W	7/13/33	332	15	11	18.0	C	—	Yes	C3+	Gangrene—thigh amputation	p m	5 days
47	1033	44	F	W	11/ 6/33	355	22	15	—	C	3	Yes	C3+	Mastoiditis with multiple abscesses	—	61 days
48	1076	37	M	W	1/10/34	372	25	11	—	C	—	Yes	C3+	Pulmonary abscess	—	15 days
49	1255	26	M	W	6/29/34	308	27	14	—	C	—	No	C3+	Dysentery	p m	67 days
50	588	26	F	W	10/2/34	260	28	8	—	C	—	Yes	C3+	Active pulmonary tuberculosis	p m	82 days
51	1304	56	F	B	11/ 2/34	420	27	39	14.1	U	1	Yes	C3+	Hypertensive cardio-vascular disease	—	12 days
52	1418	56	F	B	12/22/34	480	23	50	16.0	U	4	Yes	C3+	Hypertensive cardio-vascular disease	p m	42 days
53	1456	61	F	B	2/ 1/35	736	18	30	23.4	U	1	No	C3+	Dermatitis gangrenosa	p m	54 days
54	1473	67	M	W	2/19/35	388	21	16	25.9	U	—	Yes	C3+	Coronary occlusion	p m	16 days
55	1477	38	F	W	2/24/35	926	23	88	12.7	C	3	No	C3+	Pyelonephritis	p m	22 days
56	1515	59	F	B	3/25/35	572	29	50	23.1	C	3	Yes	C3+	Hypothyroidism	—	9 days
57	1095	39	F	W	1/12/36	688	12	22	24.8	C	1	Yes	C3+	Mastoiditis, cellulitis of face	p m	39 days
58	1899	58	F	B	4/25/36	488	13	7	46.3	C	—	Yes	C3+	Carbuncle of thigh pulmonary embolism	p m	12 days

a white woman, aged 55, admitted 11/26/36. She was rational and neither she nor her husband knew that she had diabetes. She was well until November 20 when she ate some pie which caused severe abdominal pain. On November 21 and 22 she vomited and had marked obstipation, and the next day pains in the chest. A doctor was not called until November 26. At

TABLE VII
PHILADELPHIA GENERAL HOSPITAL

Recoveries and Deaths from Diabetic Acidosis with Reference to Blood Sugar at Admission

	Below 201	201 300	301 400	401 500	501 600	601 700	701 800	801 900	901 1000	Above 1000	Average B S
AR	1	14	34	16	7	8	7	3	3	4	487
AD	1	0	3	5	4	1	8	2	4	4	713
BR	3	12	14	8	8	4	0	2	0	3	461
BD	0	3	5	11	1	2	1	1	0	3	554
C ₁ C ₂	1	7	4	9	8	6	2	2	0	0	488
C ₃	0	2	6	5	1	2	1	0	2	0	501
R	4	26	48	24	15	12	7	5	3	7	478
D	2	12	18	30	14	11	12	5	6	7	567
	R 78 D 32	29 1%		R 51 D 55	51 9%		R 22 D 30	57 7%			
R+C ₃	4	28	54	29	16	14	8	5	5	7	480
D-C ₃	2	10	12	25	13	9	11	5	4	7	580
	R 86 D 24	21 8%		R 59 D 47	44 4%		R 25 D 27	52 0%			

TABLE VIII
PHILADELPHIA GENERAL HOSPITAL

Cases of Diabetic Coma in Which the Blood Sugar Was 1000 mg % or Above

	Name	Age	Sex	Color	Date Ad- mitted	No of Ad- mission	Blood Findings on Admission			Outcome	Post Mortem
							Sugar mg %	CO. vol %	Urea N mg %		
1	T J	40	M	B	11/23/25	1	1520	21	—	Died 3 hrs	p m
2	M M	58	F	W	4/ 2/26	1	1120	—	45	Recovered	—
3	T M	27	M	W	1/12/27	5	1484	11	—	Died 8 hrs	—
4	E T	50	F	B	7/19/28	1	1060	8	30	Died 16 hrs	p m
5	H H	30	F	B	3/30/29	1	1080	11	21	Recovered	—
6	G M	28	F	B	12/11/29	1	1030	12	50	Died 25 hrs	p m
7	J J	35	M	B	1/29/30	1	1500	24	—	Died 8 hrs	p m
8	H R	31	F	B	5/14/30	2	1056	10	—	Died 6 hrs	p m
9	C R	46	F	B	6/12/31	1	1056	18	55	Recovered	—
10	S D	20	F	W	9/11/31	17	1000	16	—	Died at adm	—
11	L J	53	F	B	6/10/34	1	1028	12	—	Died 2 hrs	p m
12	M H	54	F	B	10/ 5/34	1	1008	22	95	Died 59 hrs	p m
13	M S	40	F	W	10/ 9/34	6	1000	7	20	Died 16 hrs	—
14	N D	21	F	B	12/23/34	1	1850	13	95	Recovered	—
15	F C	39	F	B	1/20/35	1	1024	15	63	Recovered	—
16	S P	56	F	W	2/28/35	1	1470	10	42	Died 2 hrs	p m
17	J P	22	M	B	3/20/35	1	1056	14	43	Recovered	—
18	G H	36	M	B	5/16/35	1	1256	18	78	Died 2 hrs	p m
19	M F	59	F	W	1/12/36	4	1080	15	75	Recovered	—
20	J T	57	M	W	2/ 6/36	3	1000	14	20	Died 20 hrs	p m
21	H M	48	F	B	2/20/36	1	1290	16	60	Died 39 hrs	p m
22	M G	45	M	W	4/29/36	2	1360	12	40	Recovered	—
23	M G	45	M	W	8/ 8/36	3	1168	17	55	Recovered	—
24	A H	52	M	W	12/15/36	1	1528	25	113	Died 6 hrs	p m
25	E G	59	F	W	12/26/36	1	1008	12	55	Died 5 hrs	—

admission it was noted that she had slight abdominal distention, no tenderness, no masses and no peristalsis. She died suddenly one and one-half hours after admission. At autopsy it was discovered that she had a ruptured appendix and peritonitis.

TABLE IX
PHILADELPHIA GENERAL HOSPITAL
Recoveries and Deaths from Diabetic Acidosis with Reference to CO₂ at Admission

	Below 11	11-15	16-20	21-25	26-29	Average CO ₂
AR	2	30	28	29	8	18.7
AD	2	19	4	4	3	16.0
BR	2	13	14	11	14	20.2
BD	4	7	6	8	2	18.0
C ₁ C ₂	2	14	7	8	8	18.8
C ₃	0	3	2	6	8	22.8
R	4	43	42	40	22	19.2
D	8	43	19	26	21	18.5
R+C ₃	4	46	44	46	30	19.6
D-C ₃	8	40	17	20	13	17.6
	66.7%	46.5%	27.9%	30.3%	30.2%	

TABLE X
PHILADELPHIA GENERAL HOSPITAL
Recoveries and Deaths from Diabetic Acidosis with Reference to
Blood Urea Nitrogen at Admission

	Below 21	21-40	41-60	Above 60	Not Done	Average B U N
AR	66	23	4	4	0	20.5
AD	6	8	8	6	4	44.7
BR	36	11	3	2	2	21.6
BD	3	10	8	3	3	43.3
C ₁ C ₂	13	13	7	3	3	35.8
C ₃	7	5	3	4	0	36.7
R	102	34	7	6	2	20.9
D	29	36	26	16	10	40.0
	22.1%	51.4%	78.8%	72.7%		
R+C ₃	109	39	10	10	2	23.8
D-C ₃	22	31	23	12	10	42.1
	16.8%	44.3%	69.7%	54.5%		

Among the 29 cases in the "BD" and "C₁C₂" groups in which post-mortem examinations were not made, it is quite likely that we have made some mistakes in diagnosing complications which did not exist. It is also just as likely that we missed complications in the "AD" group in the 15 cases in which there was no autopsy.

In the total number of cases there were many of unusual interest, two of which we feel deserve short descriptions. Patient 1594 (AD 25) is included in the AD group, although he died 21 days after admission. At postmortem examination no cause for his death could be found other than

TABLE XI
PHILADELPHIA GENERAL HOSPITAL

Recoveries and Deaths from Diabetic Acidosis with Reference to Leukocytosis at Admission

	- 10 0	10 1 20 0	20 1 30 0	30 1 40 0	40 1 50 0	50 1 +	Not Done	Average W B C
AR	6	28	23	2	5	3	30	22 2
AD	3	9	8	3	1	0	8	20 4
BR	2	23	11	2	2	2	12	21 6
BD	1	8	3	0	1	1	13	23 0
C ₁ C ₂	3	12	10	3	2	1	8	22 5
C ₃	1	6	5	0	1	0	6	21 3
R	8	51	34	4	7	5	42	22 0
D	8	35	26	6	5	2	35	21 8
R+C ₃	9	57	39	4	8	5	48	21 9
D-C ₃	7	29	21	6	4	2	29	21 9

TABLE XII
PHILADELPHIA GENERAL HOSPITAL

Recoveries and Deaths from Diabetic Acidosis with Reference to Age

	Below 11	11 20	21 30	31 40	41 50	51 60	61 70	Above 70	Average Age
AR	4	40	23	9	11	9	0	1	27 1
AD	0	3	6	6	4	11	2	0	41 8
BR	0	16	9	7	12	7	2	1	34 5
BD	1	0	1	4	6	7	8	0	49 4
C ₁ C ₂	0	2	2	3	11	11	4	6	52 6
C ₃	0	1	2	4	2	7	2	1	47 8
R	4	56	32	16	23	16	2	2	29 7
D	1	6	11	17	23	36	16	7	48 2
	R 92 D 18	16 4%		R 39 D 40	50 6%	R 20 D 59	74 7%		
R+C ₃	4	57	34	20	25	23	4	3	31 8
D-C ₃	1	5	9	13	21	29	14	6	48 2
	R 95 D 15	13 6%		R 45 D 34	43 0%	R 30 D 49	62 0%		

lesions in his brain which we have described⁵ in other cases dying from diabetic acidosis. Patient 1255 (C 49) is diagnosed "dysinsulinism". His history strongly suggested spells of spontaneous hypoglycemia at times for a period of two years. He was admitted in diabetic acidosis and took moderate doses of insulin for three weeks. He then began to have very severe

spontaneous hypoglycemia which could not be controlled Two months after admission a laparotomy was done in the hope of finding a pancreatic adenoma None was found and part of the pancreas was resected, from which he died two days later

In estimating at the time of admission the prognosis of a case of acidosis,

TABLE XIII
PHILADELPHIA GENERAL HOSPITAL
Recoveries and Deaths from Diabetic Acidosis with Reference to Sex and Color

	Male	Female	White	Black
AR	34	64	57	40
AD	10	22	22	10
BR	23	31	33	21
BD	4	23	16	11
C ₁ C ₂	7	32	29	10
C ₃	3	16	9	10
R	57	94	90	61
D	24	93	76	41
	29 6%	49 7%	45 8%	40 2%
R+C ₃	60	110	99	71
D-C ₃	21	77	67	31
	25 9%	41 2%	40 4%	30 4%

TABLE XIV
PHILADELPHIA GENERAL HOSPITAL
Recoveries and Deaths from Diabetic Acidosis with Reference to Mental State at Admission

	Conscious	Unconscious
AR	87	10
AD	5	27
BR	49	5
BD	11	16
C ₁ C ₂	20	19
C ₃	17	2
R	136	15
D	53	64
	28 0%	81 0%
R+C ₃	153	17
D-C ₃	36	62
	19 0%	78 5%

first of all we should like to know what complication may be present and its severity Of the 139 cases with complications, 85 died, a mortality of 61 2 per cent As we have already pointed out, it often happens that no judgment can be formed as to the part a complication is playing until after the patient has been under treatment a considerable period of time, and the very presence of a complication may not be suspected until the postmortem ex-

amination. It is only in cases in which the complication is fairly evident at the time of admission that the question of a complication can be given much consideration in estimating the prognosis. Our procedure in this report has been to group the cases according to the outcome of the cases, and then to examine the data which were known within the first hour after admission in order to estimate what inference regarding prognosis may be drawn from each datum.

Blood Sugar (table 7). The degree of hyperglycemia is not usually considered to have much effect on mortality. Certainly no one believes that diabetics die from high blood sugar. But when the blood sugar is very high the factors which do cause death are more likely to be present. The mortality for all the cases in which the blood sugar was above 700 was

TABLE XV
PHILADELPHIA GENERAL HOSPITAL
Recoveries and Deaths from Diabetic Acidosis with Reference to
Hours in Acidosis at Admission

	Below 13	13-24	25-48	Above 48	Not Known	% Cases above 24 hrs
AR	14	18	21	19	25	55.5%
AD	3	4	10	11	4	75.0%
BR	8	6	15	9	16	63.2%
BD	1	3	6	13	4	82.6%
C ₁ C ₂	3	5	9	12	10	72.4%
C ₃	4	1	4	2	8	54.5%
R	22	24	36	28	41	58.2%
D	11	13	29	38	26	73.6%
	33.3%	35.1%	44.6%	57.6%		
R+C ₃	26	25	40	30	49	
D-C ₃	7	12	25	36	18	
	21.2%	32.4%	38.5%	54.5%		

57.7 per cent, whereas for the cases for which it was 400 or lower, it was 29.1 per cent. If the "C₃" cases be regarded as recoveries, the mortality was 52.0 per cent and 21.8 per cent respectively, about two and one-half times as high in the high blood sugar group as in the low one. Among the uncomplicated cases it may be pointed out that the average blood sugar in the "AR" group was 487, and in the "AD" group 713. When the blood sugar is very high, therefore, we are justified in anticipating a higher mortality than when it is low.

We have previously published ⁴ 16 cases in which the blood sugar was 1000 or above, the first case occurring in 1925. We now add nine additional ones (table 8). Of the total of these cases nine recovered and 16 died. Case 10 does not appear in tables 2 to 6 as she arrived in the receiving ward moribund and died a few minutes after her blood had been taken and sent to the metabolic laboratory. Case 14 had a blood sugar of 1850,

the highest in the literature in which recovery occurred Cases 22 and 23 are the same individual, a white man aged 45

CO₂ Volume Per Cent (table 9) The degree of chemical acidosis is measured by the CO₂ combining power measured in volumes per cent As might be anticipated, the mortality is higher the lower the CO₂ This becomes clear, however, chiefly in the uncomplicated cases The presence in the total series of a large number of cases with severe complications masks the effect of the acidosis

In determining a criterion of acidosis according to which the selection of cases for this report might be made the level of 29 volumes per cent CO₂ was selected for the following reasons The unusual figure 29, instead of some multiple of five or ten, comes about by virtue of the fact that many years ago our laboratory began to keep its CO₂ files in groups of 10, 60 to 69, 50 to 59, etc We feel justified in including the group 20-29, because in this group out of 109 cases there were 47 deaths, in seven of which no other cause of death was found

At the low extreme our chemists have reported no value lower than six The analyses are made routinely within 20 minutes after the blood is withdrawn When the observed volume of gas is very low, in addition to technical difficulties is the fact that the corrections become larger than the final result, and therefore of relatively great importance The chief difficulty, however, is that when the CO₂ combining power is as low as 2 volumes per cent, as reported by several observers, the corresponding alveolar CO₂ tension, at a pH compatible with life, should require a ventilation rate of approximately 40 liters per minute in order to rid the body of the CO₂ of metabolism This is a matter for the chemists to settle, and from the clinical point of view is only of academic interest

Blood Urea Nitrogen (table 10) The effect of an abnormal blood urea nitrogen is more striking than either an increase in blood sugar or a decrease in CO₂ As the blood urea nitrogen increases above 20 mg per cent the mortality increases rapidly In the total series the mortality for cases with 20 mg and below was 22.1 per cent, whereas for those cases with more than 20 mg the mortality was 62.4 per cent This increase in mortality is also clearly seen in the uncomplicated cases, being 8.3 per cent for the cases of 20 mg and below, and 41.5 per cent for the cases of 21 mg and above The average blood urea nitrogen in the "AR" cases was 20.5 mg per cent and the average in the "AD" cases 44.7 mg per cent

Leukocytosis (table 11) In 77 cases the white blood count is not included in this report, either because it was not done or because it was not done until some hours had elapsed after treatment was begun The white count usually drops rapidly as treatment progresses In the 191 cases in which a white count was made at admission it is noteworthy that it was above 10,000 in all but 16 cases There is no correlation between the degree of leukocytosis and the mortality More important is the fact that the

degrees of leukocytosis seem to be about the same for the uncomplicated cases and for those in which complications are present. Even when the leukocytosis is marked, it does not add to the evidence in favor of a complication. There were 19 cases with white counts above 40,000 of which nine were uncomplicated and 10 had complications, which is almost exactly the ratio of complicated-uncomplicated cases in the entire report (129 to 139). The two highest counts were on patients 1827 (AR 83) 72,100 and patient 287 (BD 8) 73,200.

Age (table 12). The increase in mortality with advancing years is very striking. This increase is due in part to the larger amount of death-dealing complications which begin to appear at about age 40, and in part to the inability of older patients to withstand the acidosis itself. The total mortality for patients up to 30 years was 16.4 per cent while for those over 50 years it was 74.7 per cent, with the " C_1 " cases regarded as recoveries, 13.6 per cent and 62.0 per cent respectively. Of the "A" cases 30 years of age and under, 67 recovered and nine died, of these nine, seven were unconscious when admitted and six had been in acidosis over 24 hours. On the other hand, of the cases over 50 years of age 10 recovered and 13 died. The average age for the "AR" group was 27.1 years and for the "AD" group 41.8 years. The average of all 268 cases was 37.8 years.

Sex and Color (table 13). There are 81 males and 187 females in this series, the total mortality being 29.6 per cent for the males and 49.7 per cent for the females. In the uncomplicated cases the mortality is only a little larger for the females. In the "BD," " C_1C_2 " and " C_1 " groups, however, there are 71 females and only 14 males. This disproportionately larger number of females is hard to account for. It is not due to diseases of the female organs. It is our impression that the presence of this great number of serious complications in women is due to greater negligence and less willingness to go to a hospital until driven to it. Our experience with our entire clinic, however, is that once in the hospital the women are more anxious to stay on than the men.

The population of Philadelphia is 11.3 per cent colored and the patients admitted to the metabolic division are approximately 20 per cent colored. In this report there are 166 white cases in 144 patients and 102 colored cases in 80 patients. The incidence of acidosis is, therefore, about two and one-half times as great in our colored patients. The mortality, however, is somewhat lower in the colored, but this is mostly accounted for by the greater percentage of return cases. Of the 44 return cases, 22 are white and 22 colored, two white cases died and one colored.

Mental State (table 14). The cases have been divided into conscious and unconscious groups, according as to whether it was possible to arouse them sufficiently to answer "Yes" or "No" to some simple question. The importance of the mental state in the prognosis is very great. The total mortality for the conscious patients was 28.0 per cent and for the uncon-

scious patients 81.0 per cent, with the "C₃" cases regarded as recoveries 19.0 per cent and 78.5 per cent. In other words a conscious patient is about four times as likely to recover from the acidosis as an unconscious one. In the uncomplicated cases, only 5.4 per cent of the conscious cases died whereas 73.0 per cent of the unconscious cases died.

Hours in Acidosis (table 15). We have been able to tabulate the cases according to the duration of the acidosis only in general terms. Even if an accurate history is available, when, from the history alone, may a patient be said to begin to be in acidosis? We have taken as our criterion the onset of nausea and vomiting, or when this symptom was not mentioned in the history or not present, we have taken the statement that the patient definitely became drowsy. In 67 cases it was impossible to make any estimation. According to the duration of the acidosis the cases have been divided into four groups: (1) Up to 12 hours, (2) 13 to 24 hours, (3) 25 to 48 hours, and (4) 49 hours and above. As might be expected the mortality increases rapidly with the duration of the acidosis as shown in table 15.

There are, of course, other important clinical data which aid in estimating the prognosis, chief of which is the state of the cardio-vascular system. When the blood pressure is very low at admission or falls during the course of treatment, this is of very evil omen. We have not been able to present this in the form of a table. Of great importance, also, is the rapidity with which a patient responds to treatment. We are confining ourselves in this report, however, to the data which are available during the first hour after admission.

It is obvious from the above data that a much more accurate prognosis can be given from the clinical data than from the laboratory data. In estimating the prognosis of a given patient or in comparing the mortality of one series of comas as compared with some other series, it is far more important to know the complications present, the mental state, the age of the patients, and the duration of the acidosis, than it is to know the blood sugar, the CO₂, and the urea nitrogen. As regards treatment, however, frequent estimations of the blood sugar and CO₂ during the course of the acidosis are indispensable in properly gauging the doses of insulin and glucose.

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HYPERTHYROIDISM IN THE NEGRO *

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A REVIEW of current literature and monographs which deal with diseases of the thyroid gland gives definitely the impression that hyperthyroidism is uncommon in the negro ^{1,2}. We have been impressed with the fallacy of this current belief. From the files of the St. Philip Hospital † for negroes we have selected records of 37 patients admitted during the past five years which justify an unequivocal diagnosis of Graves' disease.

Twenty-seven of the patients lived in the city of Richmond and the remaining 10 in the adjoining counties, this entire section of Virginia is geographically a tidewater area and is distinctly a non-endemic goiter zone.

Throughout the period of this study we have been impressed with the fact that hyperthyroidism in the negro is invariably definite and characteristic in its clinical manifestations. The symptoms begin abruptly, invariably pursue a progressive course with increasing intensity, spontaneous remissions rarely if ever occur, and iodine induced remissions are of brief duration.

Regardless of age, the clinical behavior of the patients and the observed physical phenomena were characteristically typical of the Graves' syndrome (figure 1). In only one patient was there made the diagnosis of thyroid adenomata with hyperthyroidism. In the remaining 36 patients the clinical picture was that of exophthalmic goiter. That this clinical impression was correct is substantiated by the histologic changes observed in the glands removed surgically. Thirty-three of the 34 specimens showed varying degrees of diffuse hyperplasia.

In addition to the usual symptoms and signs observed in Graves' disease, others of peculiar interest are frequently present in negro patients. The most characteristic and constant phenomena occurring in the finger nails are illustrated in figure 2. The nails are brittle and thin, but stiff, and, when the examining finger is drawn across the edge, it causes the sensation as of scraping the sharp edge of a razor blade. The nails become undermined and there is a definite line of pigmentation at the point of fusion of the excavated and non-excavated portion.

We have followed many of the patients after the basal metabolism was reduced to normal by a subtotal thyroidectomy and observed a disappearance of the abnormality of the nails with an improvement of general nutrition ‡.

* Read at the St. Louis meeting of the American College of Physicians, April 21, 1937.
From the Hospital Division, Medical College of Virginia, Richmond, Virginia.

† St. Philip Hospital, a part of the Hospital Division of the Medical College of Virginia,
is for negro patients only.

‡ These changes occur also in the white race, but are neither so constant nor so evident.



FIG 1 Illustrating our conception of Graves' disease in a negro

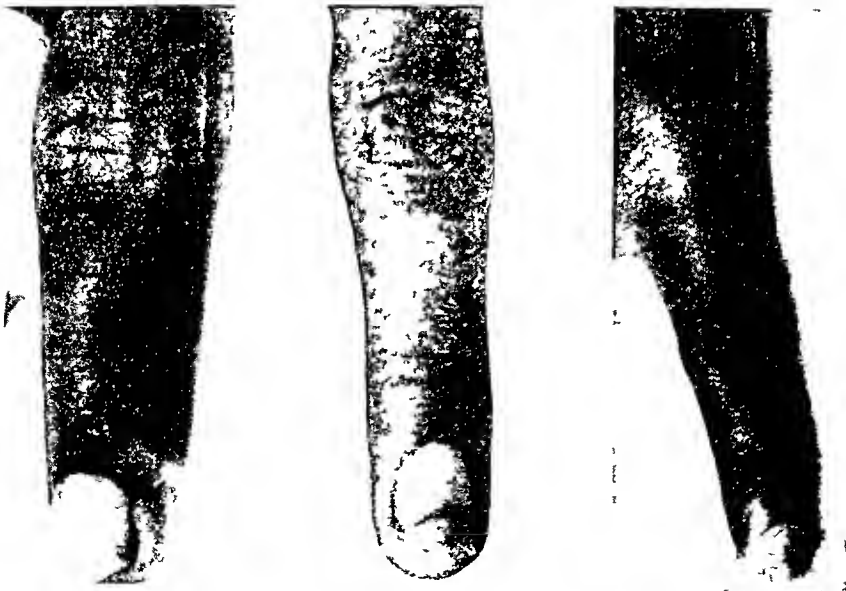


FIG 2 The nail changes in exophthalmic goiter Note that manicuring has not altered the basic characteristics

Pigmentation of the nails (figure 3) is frequent but by no means typical of hyperthyroidism, for it is prevalent in a variety of nutritional maladies and is occasionally present in healthy individuals



FIG 3 Pigmented nails See text

The skin is peculiarly thin, the wrinkles very fine and the texture is of a velvety quality (figure 4) The skin phenomena are best observed on the back of the hands and the flexor surface of the forearms and are strikingly



FIG 4 Note the fine texture of the skin

different from the dry coarse skin noted in other non-febrile nutritional maladies seen frequently in negro patients living in this section of the country

Twenty of the 37 patients were subjected to intensive cardiovascular study with the aid of teleroentgenograms, electrocardiograms and the usual clinical methods The data are tabulated in table 1 Of these so studied,

13, or 65 per cent showed cardiothoracic ratios greater than 50 per cent. In nine of the 13 patients who had roentgen-ray evidence of cardiac enlargement, hyperthyroidism was the only demonstrable factor responsible for the observed change. There existed neither arterial hypertension nor the phenomena of valvular disease, and all of these patients were less than 40 years of age, varying from 15 to 39 with an average age of 29 years.

Electrocardiograms were made on 22 patients (table 1). Fifteen, or

TABLE I

Case	Age	Sex	B M R	Pulse Rate per Min	Blood Pressure		Cardiothoracic Ratio	Electrocardiogram and Remarks
					Systolic	Diastolic		
1	15	F	+97	138	130	60	55%	Electrical axis, left preponderance, high T ₁ , T ₂ and T ₃ take off
2	30	F	+39	156	144	84	43%	T ₁ , T ₂ , and T ₃ inverted
3	20	F	+34	167	138	70	48%	T ₂ and T ₃ inverted
4	38	M	+38	150	134	65	59%	Auricular flutter, electrical axis, left preponderance, marked Congestive failure, rheumatic heart disease, mitral valve, rhythm restored to normal
5	28	F	+60	125	120	60	57%	Electrical axis, right preponderance Congestive failure, rheumatic heart disease, mitral stenosis
6	59	M	+87	128±	160	80	55%	Auricular fibrillation, electrical axis, left preponderance Congestive failure, marked generalized arteriosclerosis, rhythm restored to normal
7	39	F	+47	150	155	65	56%	Auricular fibrillation, T ₁ and T ₂ inverted Rhythm restored to normal
8	29	F	+60	132	144	60	53%	Electrical axis, left preponderance, marked
9	48	F	+62	112	154	80	55%	Electrical axis, left preponderance, marked
10	38	F	+40	125	150	80	57%	T ₂ iso-electric, electrical axis, left preponderance
11	35	F	+36	107	150	20	54%	T ₂ diphasic, electrical axis, left preponderance, rheumatic heart disease, aortic valve insufficiency
12	25	F	+66	125	160	70	46%	Electrical axis, left preponderance, marked
13	32	M	+40	115	165	65	49%	S ₃ deep and notched Electrical axis, left preponderance
14	33	M	+55	160±	140	60	69%	Auricular fibrillation Congestive failure, rhythm restored to normal P-R interval 0.24 sec
15	25	F	+55	118	130	75	60%	Electrical axis, left preponderance
16	32	F	+95	110	130	50	51%	Normal
17	22	F	+37	115	140	80	41%	Normal
18	39	F	+48	117	128	55	Data lacking	Normal
19	21	F	+66	125	155	60	51%	Normal
20	22	F	+86	140	140	70	49%	Normal
21	23	F	+41	132	144	55	Data lacking	Normal
22	27	F	+32	122	130	65	44%	Normal

68 per cent showed significant deviations from the normal and in only four of these did there occur vascular or endocardial disease which could reasonably have been responsible in part for the abnormal changes

That there is a striking tendency for the heart to resume a normal functional state following relief of hyperthyroidism is clinically impressive. A study is in progress to determine whether electrocardiographic changes and cardiac enlargement disappear with the restoration of normal health.

The 15 patients who were not studied either with the roentgen-ray or the electrocardiograph varied in age from 12 to 60 with an average age of thirty-four. Six of the 15, or 40 per cent, had physical phenomena indicative of cardiac enlargement. Three of these had arterial blood pressure definitely above normal: in one 180 systolic, 112 diastolic, another 200 systolic, 124 diastolic, and another 170 systolic, 110 diastolic. All in this group maintained a sinus rhythm while in the hospital and none had the physical signs of either endocardial disease or congestive heart failure.

It is usually assumed that a low diastolic blood pressure is common in hyperthyroidism. In this group of patients with basal metabolic rates varying from plus 25 to plus 97 with an average of plus 51, the lowest diastolic blood pressure was 50 mm Hg,* the highest 120 mm Hg with an average of 72.05 mm Hg. The absence of striking reductions in diastolic pressure may reflect the racial characteristics of the vascular system of the negro, for it is becoming increasingly evident that hypertension occurs at a lower age level in the negro than in the white race, and that there is a much greater tendency for the disease to run a malignant clinical course.

Thirty-four patients were treated surgically following a preliminary period of preparation. Lugol's solution, 30 drops a day, bed rest and phenobarbital, as a sedative when indicated, were the routine measures used during the pre-operative treatment. This was extended over an average period of 13 days. There were four postoperative deaths: one due to pneumonia, two to postoperative wound infection with a *Streptococcus hemolyticus* septicemia, and one a sudden death with the cause not definitely determined but attributed to pulmonary embolism.

One patient left the hospital after refusing surgical treatment. Two patients died from hyperthyroid crisis soon after entering the hospital. The total mortality was six of the 36 cases treated, a percentage of 16.6 per cent. This is an extremely high mortality, and a detailed analysis of the deaths is instructive. The death of the two patients from streptococcus septicemia was preventable and was not related directly to the hyperthyroidism.

The patient who succumbed supposedly to pneumonia two days after the operation had only five days of pre-operative iodine therapy and was operated on by a surgeon with very limited experience in thyroid disease when the basal metabolic rate was plus 61. A review of the hospital record clearly shows that postoperative hyperthyroid crisis was the immediate cause of

* Case 11 omitted due to the existence of aortic regurgitation.

death With adequate pre-operative therapy and skilled operative technic, the operative mortality would have been only one of the 34 treated surgically, a mortality of 2.9 per cent

It is highly significant that two patients died from the effects of acute hyperthyroid crisis before the hyperthyroidism could be controlled with iodine and before surgery was attempted If one eliminates the clearly preventable fatal operative complications, he finds that two patients died without any attempt at surgical relief while only one died following thyroidectomy These facts need emphasis for there are those who, because of their fear of the operative mortality, are inclined to withhold surgical therapy In this group of patients the "medical" mortality was higher than the "surgical," if one eliminates the deaths incident to faulty surgical technic

During the same period of time covered by this study, 71 white patients were treated for hyperthyroidism at Memorial Hospital^{*} without a fatality All of these had a subtotal thyroidectomy preceded by medical preparation similar to that used routinely with the negro patients No case had, either before or after operation, a hyperthyroid crisis This comparison clearly indicates that hyperthyroidism is a more serious problem in the negro than in the white patient, not because of a fundamental difference in the nature or severity of the disease, but rather because of delay in seeking adequate treatment

COMMENTS

The occurrence of hyperthyroidism in an area almost entirely free of endemic goiter is of peculiar significance for it naturally stimulates an inquiry into the causes which operate in bringing about the condition That the factor, or factors, are potent in their effect on the negro is definitely proved by the study, for Graves' disease is proportionately as common in the negro in this area as in the white race

If there is a difference in the reaction of the negro and the white patient to hyperthyroidism, it is probably a quantitative rather than a qualitative one for our impression is that the negro has less ability to adjust himself to the disease This is particularly true of the cardiovascular apparatus, yet, in estimating the effects of increased metabolism on the heart, one must reckon not only with the percentage increase of oxygen requirements, but with the state of the peripheral vascular tonus and energy expenditure due to physical effort There was not the usual lowering of diastolic blood pressure in the negro patients observed in this study, and the occupations of all the patients required more physical effort than that required in a similar group of white patients

While these facts are undoubtedly important in exaggerating the effects of hyperthyroidism on the heart, they do not adequately explain the high percentage of significant alterations found in negro patients

^{*} For white patients only, similar staff at both hospitals

The other most significant differences in the reaction to hyperthyroidism as observed in the negro are the phenomena referable to the nervous system. While the basal metabolism is elevated, restlessness, tremor and the usually observed phenomena of stimulation are characteristically evident and of great severity, yet, relief is prompt and complete as soon as the hyperthyroidism is controlled. The average patient is entirely free of all symptoms within two weeks following subtotal thyroidectomy and we have not observed a single negro patient who required a prolonged period of convalescence for the nervous system to adjust itself. This is undoubtedly an index to the nervous mechanism characteristic of the negro.

In a recent study by one of us³ of bichloride poisoning, it was noted that there had been admitted to the Hospital Division of the Medical College of Virginia 71 patients in whom corrosive poisons had been taken with suicidal intent. There was only one negro patient in the group and she was a mulatto school teacher.

The negro is distinctly an emotional type of individual, but he has few inhibitions, hence, outlets are free and easy with the result that suicide is rare and probably for the same reason the effects of thyroxin trauma quickly disappear following the relief of hyperthyroidism.

To postulate a pathogenetic concept of Graves' disease from this study of the malady in the negro living in a non-endemic goiter area is not possible with the present lack of any common understanding concerning the real nature of the disease.

We do not believe that the "stress of modern civilization" is a factor, for, though the negro's economic stress is great, his philosophy assures complete adaptation, and emotional trauma is rarely deep or lasting in its effect.

The rarity of endemic goiter in this area quite definitely outlaws the idea of an absolute iodine deficiency as an important etiological factor. The more recent observations of Marine⁴⁻¹⁴ strongly indicate that diet can and may be a significant factor in the pathogenesis of the Graves' syndrome. From this study it is not reasonable to suggest what nutritional factors, if any, operated in the production of exophthalmic goiter in the negro living in a geographic area where endemic goiter is rare, yet, the probability of such an etiological factor is intriguing.

In the negro patients seen in the Out-Patient Clinic and hospital wards there are prevalent quite evident nutritional defects which are traceable to a diet high in carbohydrates, not adequately supplied with complete proteins and milk, woefully lacking in vegetables and fruits, and frequently deficient in total calories. Though this be true, it is not possible to assemble even circumstantial evidence incriminating any specific essential food deficiency. In the final solution of the pathogenesis of exophthalmic goiter, it is probable that many factors will be found that operate jointly in precipitating the syndrome. It is certain that iodine deficiency and the trauma of "modern life" are not the sole factors concerned.

CONCLUSIONS

1 Hyperthyroidism is a relatively common malady in the negro living in this geographical area

2 The disease manifests itself clinically as typical Graves' disease and is accompanied by a diffuse hyperplasia of the thyroid gland

3 The cutaneous changes are of peculiar interest and of real diagnostic importance

4 The cardiovascular apparatus of the negro patient suffers greatly from the effects of hyperthyroidism largely because of delay in seeking adequate treatment

5 Some factors other than primary iodine deficiency or the stress of urban life must be found to explain adequately the pathogenesis of exophthalmic goiter This study leaves the question of specific etiology unanswered

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THE ACUTE AND SUBACUTE PULMONARY INVOLVEMENT IN RHEUMATIC FEVER WITH NOTES ON THE COMPLICATION OF BASAL PULMONARY COLLAPSE¹

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THERE has been in recent years a renewed interest in the pulmonary lesions of rheumatic fever. Rabinowitz¹ (1926), basing his opinion upon clinical data, felt that there was a distinct rheumatic pneumopathy. In conjunction with Eiman, in 1927, we described certain previously unrecorded gross and histologic pulmonary lesions occurring in rheumatic fever,² and we elaborated upon these in 1932.³ We concluded that pulmonary involvement in rheumatic fever was common and the changes specific. In the meantime, other reports appeared in England (Naish, 1928⁴, Fraser,⁵ 1930), based on independent observations and with similar conclusions.

We judge by the references that come to our attention that the view that rheumatic fever involves the lungs and produces characteristic changes is being more and more widely held, though this view is by no means universal. Our own continued study of this subject, both clinical and pathologic, has increased our conviction that such is the case and that involvement of the lung to some degree in rheumatic fever is as common as that of the heart. We further feel that the acute pulmonary changes lead to permanent alterations and that the latter play a very important rôle in the strain and ultimate defeat of the right ventricle, which has heretofore been ascribed to the mechanical influence of mitral stenosis alone. We hope soon to present the evidence for this belief.

If this conception of the influence of the rheumatic pulmonary lesions on the course of rheumatic heart disease be eventually borne out, it is obvious that the rheumatic pneumopathies will take on a very important aspect. With this in mind, we wish to review the clinical picture caused by the acute lesions, to compare it with that of other common lung inflammations, from which it differs considerably, and also to add a brief comment on an interesting complication that develops in the acute and subacute phases, namely, an "inflammatory collapse" of lung tissue. Our concept of the clinical picture of the rheumatic pneumopathy has been formed by study of more than 25 patients, in whom necropsy revealed cardiac and pulmonary lesions. The pathologic changes are similar to those described in previous articles and will not be discussed here.

The degree and extent of pulmonary inflammation vary greatly with a correspondingly wide variation in the clinical picture. It is an interstitial

* Received for publication April 16, 1937.

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inflammation, which in severe involvement is accompanied by alveolar exudate giving rise to frank consolidation, the physical signs are then indicative of pneumonia. In the majority of cases, the involvement is moderate to slight, the interstitial pneumonitis being less intense, confined to smaller areas and accompanied by little and patchy alveolar consolidation. In such cases the physical signs are less conspicuous and often the pulmonary lesion is revealed only by necropsy.

Lung involvement usually appears shortly after the onset of polyarthritis, occasionally precedes it, and in many instances, especially in children, it may dominate the clinical picture from the beginning, the arthritic phenomena being slight or indeed entirely absent. In such cases the latter development of pericarditis and endocarditis will reveal the rheumatic nature of the infection. This type of pneumonia does not depend upon the presence of bronchitis after the fashion of ordinary bronchopneumonia but will often follow as do the other types of acute rheumatism, shortly after the development of sinusitis, nasopharyngitis, and tonsillitis, as a part of the widespread systemic reaction to streptococcic infection.⁶ It should not be regarded as a complication of rheumatic fever, rather is it an integral part of that disease, as much so as endocarditis.

The Clinical Picture of Rheumatic Pneumonia and Pneumonitis The pulmonary involvement is usually insidious, there being little in the appearance of many patients that would direct the physician's attention to the possible existence of pneumonia. Examination of the lungs will often reveal not only in children and adolescents, but also not infrequently in adults with acute rheumatic fever, areas of bronchial breathing and dullness on percussion, suggestive of consolidation. The bronchial breathing is sometimes loud, at other times muffled and distant, in some patients expiration lacks the exquisite high pitch heard over the consolidation of pneumococcus lobar pneumonia. So-called acute emphysema will sometimes be present, due to an acute inflammatory turgescence of the lung tissue. These signs are best elicited posteriorly over the lower lobes, they are often conspicuous at the angle of the scapula, and to a lesser degree are found in the axillary areas. The upper lobes are not immune to involvement. Where bronchial breathing is pronounced, egophony and whispered pectoriloquy may be noted. Râles may or may not be present, they are of variable quality, and are seldom heard in the same number and intensity as in pneumococcus lobar pneumonia. There are, however, occasional cases in which the physical signs of consolidation are almost identical with those found in pneumococcus pneumonia. The similarity exists for only a short time because the transient character of the rheumatic lesion is in striking contrast to the orderly and progressive resolution of the pneumococcus consolidation. What on one day appears to be characteristic consolidation with tubular breathing may appear within the next day or two as an atelectasis with very distant tubular breathing or often with an absence of breath sounds. The signs of con-

solidation may appear in another lobe, in some patients the successive involvement and abatement in a number of areas suggest an analogy to the course of the polyarthritis. Consolidation may recur in the same area within a few weeks in virulent cases. In many patients the physical signs of pulmonary involvement, while unmistakable, suggest that the inflammatory reaction has not gone on to true consolidation since typical bronchial

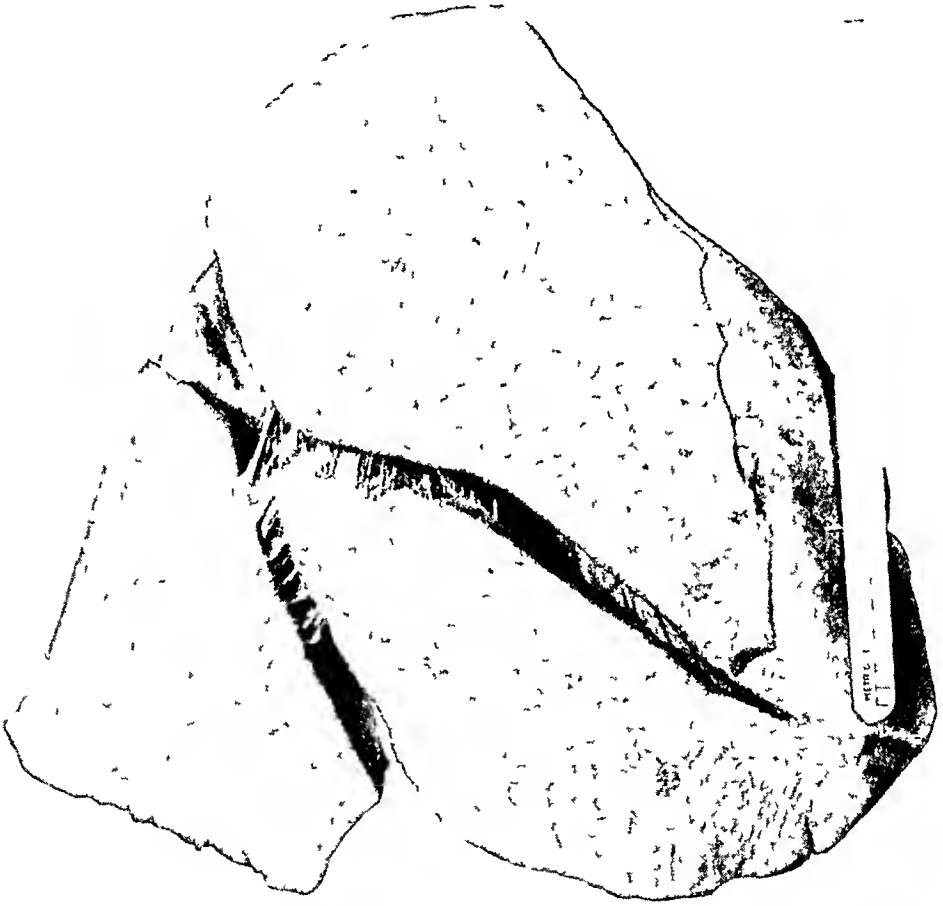


FIG 1 Right lung from a case of rheumatic pneumonitis, subacute stage showing basal collapse. Note marked diminution in size of the lower lobe. There was a small effusion in both pleural sacs and an acute pericarditis with 250 c.c. of exudate. The effect of the latter on the production of a right sided collapse was probably negligible.

breathing is absent—indeed more frequently the breath sounds are distant or obscured by râles. In such cases the term “pneumonitis” will be preferred by many physicians. This milder degree of involvement is probably that which is most commonly encountered.

There is a surprising disproportion in most cases between the symptoms and the physical signs, even when the pulmonary involvement is fairly extensive. A comparison with the clinical course of pneumococcus lobar pneu-

monia will emphasize this point. The classical picture of lobar pneumonia calls for an initial chill, prolonged and high fever, usually severe pleural pain, rusty sputum, marked elevation of the respiratory rate and crisis, these are not observed in rheumatic pneumonia and their absence is largely the reason for the tardy recognition of an important clinical phenomenon. The initial chill that signalizes the onset of pulmonary invasion has not been noted, or at least is not striking enough to achieve distinction from the mild chilliness that recurs from day to day in some rheumatic fever patients. There may

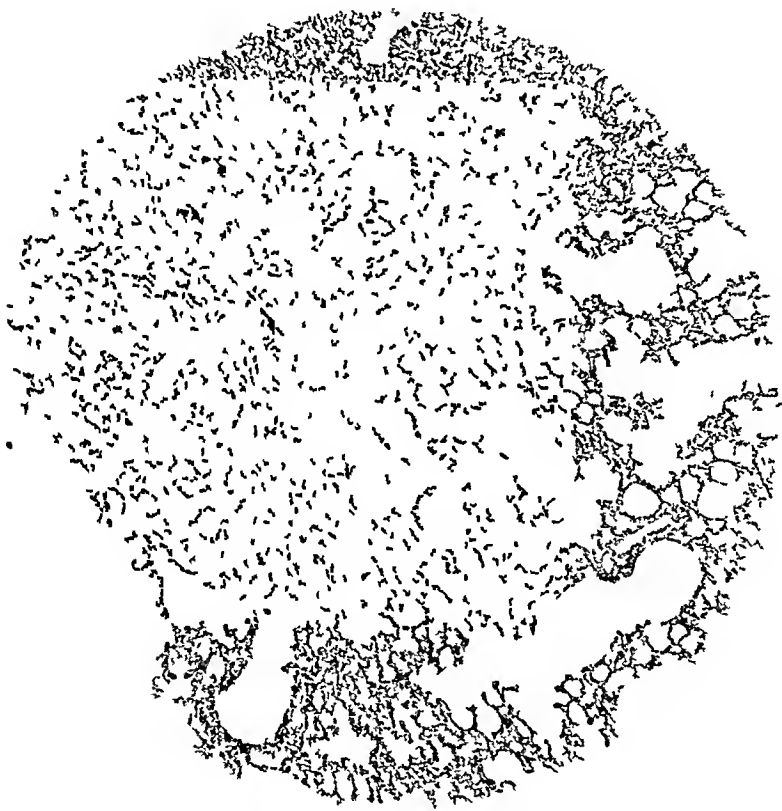


FIG 2 Lobular atelectasis developing in the course of acute interstitial rheumatic pneumonitis ($\times 33$)

or may not be a cough, if present it is rarely troublesome, and never very productive. In some cases, the sputum is blood streaked, which may be ascribed by the attending physician to passive congestion secondary to cardiac failure, though it probably has its origin in the hemorrhagic alveolar exudate of the pneumonia. The sputum does not present any special bacteriological findings. Pneumococci may be found, but not as a predominant organism, streptococci, both of the hemolytic and of the viridans strains, will often be present. Such findings may represent only the bacterial flora

of the nasopharyngeal sinus or tonsillar infection, few organisms, often none at all, are found in the inflamed lung tissue

The absence of respiratory distress in most patients is striking. Expiratory grunt and the play of the nostrils, common in lobar pneumonia, are seldom present. The respiratory rate is slightly or moderately elevated, irregularly so. This is all the more remarkable in view of the fact that a serious myocarditis often coexists. In occasional cases where both lungs

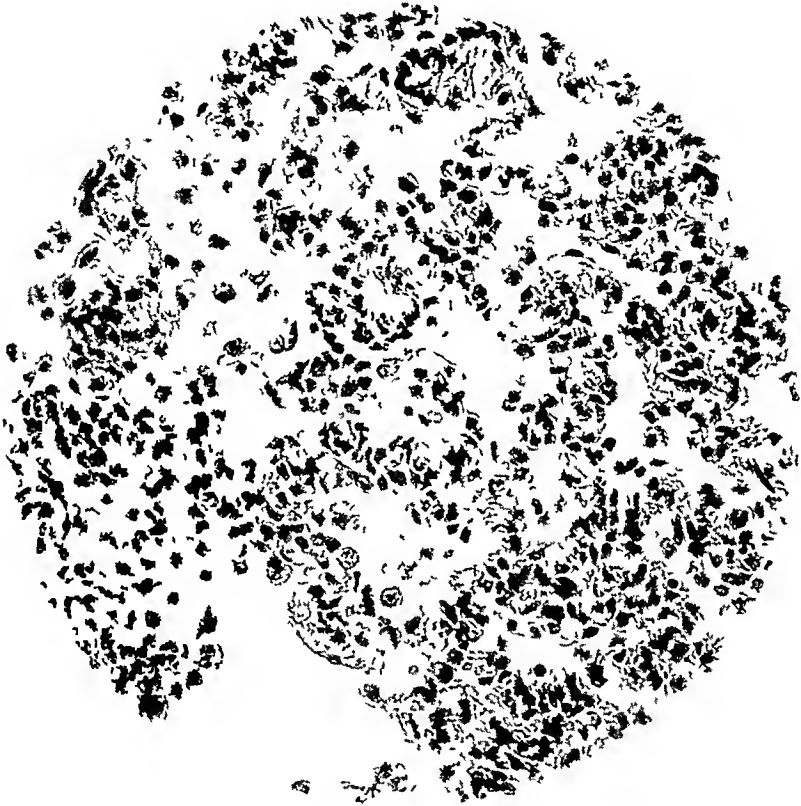


FIG 3 Early congestive phase of acute interstitial pneumonitis showing marked capillary congestion, early interstitial infiltration of endothelial cells and beginning collapse. There was no obstructive change in the bronchial tree ($\times 276$)

are almost entirely consolidated, the respiratory rate will quickly rise in what usually develops to be a terminal phase.

Pleural pain is relatively rare. Most patients never complain of it, but, in contrast, a considerable number have substernal pain due to pericarditis. Fibrinous pleurisy, often observed at necropsy,⁷ has been accorded a degree of importance in the literature which is not altogether warranted by its observable clinical manifestations. While friction rubs are not uncommon, pleural pain, curiously enough, has been encountered only in the minority of patients with pulmonary consolidation. In only two instances in a series of

25 patients was lancinating pleural pain the striking initial feature—as it so commonly is in pneumococcus pneumonia. Empyema as a direct complication has not been present either clinically or in the cases that we have seen at necropsy. Its rarity in rheumatic fever was pointed out many years ago by Longstreth *⁸

The fever is usually moderate, in some instances high, but very irregular

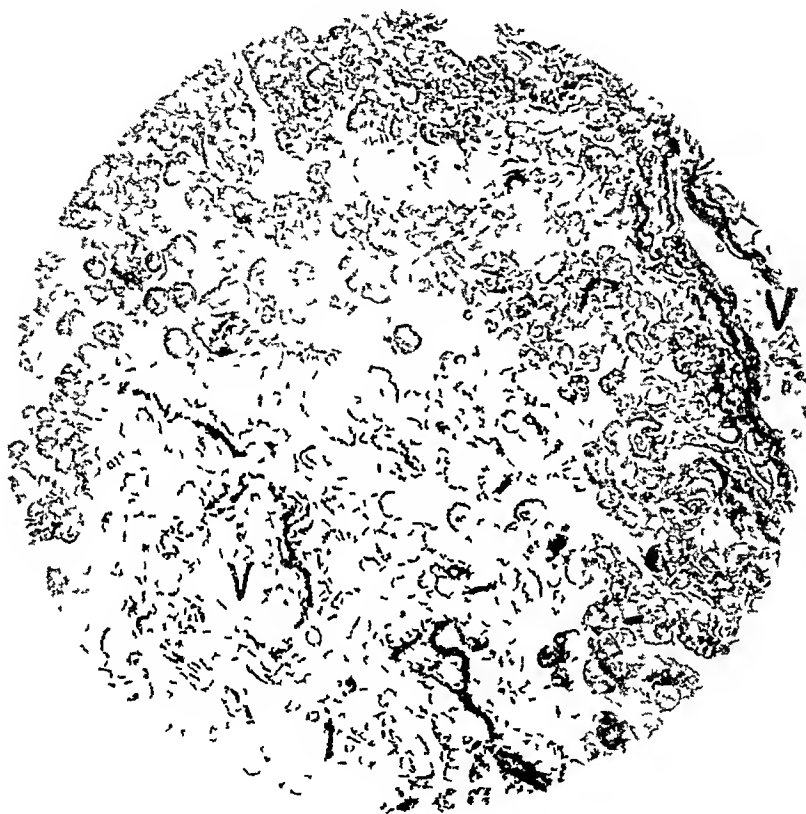


FIG 4 Showing early acute interstitial rheumatic pneumonitis and beginning collapse. Note acute destruction of the elastica, it is preserved in the walls of the small veins (V) but has practically disappeared from the interstitial alveolar structure, a few dark stained shreds and granules remaining (Weigert stain) ($\times 276$)

(102 to 105°), and probably related to the systemic infection rather than to the local pulmonary changes. Our experience does not coincide with that of Naish who was impressed by the minor character of the febrile elevation in most of his cases. It is possible that salicylate therapy may have been partly responsible for this difference, usually the presence of marked pulmonary involvement is associated with a severe type of infection, in which the febrile reaction is considerable. There is no crisis, the fever follows the

* Morris Longstreth, Pathologist (1872-1879) and Visiting Physician to the Pennsylvania Hospital (1879-1895)

irregular course seen in such severe cases, and gradually falls in proportion to the general recovery from the rheumatic disease

In most cases the pulmonary involvement is obscured by the generally severe symptom complex that is known as acute rheumatic fever, and apparently adds little to the already existent toxicity. There is a small group of patients in whom the pulmonary invasion is extremely rapid and widespread, accompanied by quickly developing dyspnea and cyanosis. In such

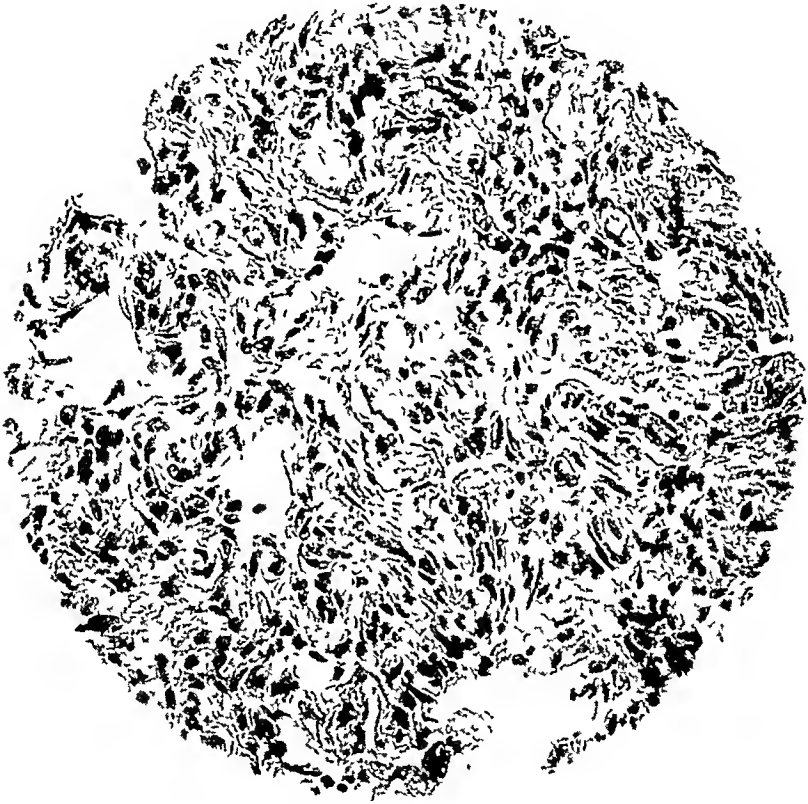


FIG 5 Showing subchronic interstitial rheumatic pneumonitis complicated by excessive interstitial fibrosis in a collapsed area. It is doubtful whether such lung tissue can ever regain its pre-inflammatory resiliency ($\times 276$)

instances the pulmonary involvement can suddenly alter the prognosis and can be regarded as the actual cause of death

The rheumatic and the pneumococcic pneumonias can co-exist in the same lung, but our necropsy experience suggests that such occurrence is distinctly uncommon. The ordinary type of bronchopneumonia may co-exist or occur as a secondary infection, but this association is also, we think, uncommon. The large majority of rheumatic fever patients with lung involvement do not have a history of preceding bronchitis, nor do they have

the purulent expectoration or diffuse bronchial moisture usually noted in cases of suppurative bronchitis or the common type of bronchopneumonia

Laboratory Data The laboratory data differ in no way from those usually recorded in rheumatic fever, namely, a leukocytosis of 10,000 or more, occasionally mounting as high as 25,000, the differential count usually shows a moderate increase in both neutrophils and monocytes. Blood cultures were done in only a few cases and were always negative.

Roentgen-ray examination of the chest is often disappointing. Areas of moderately increased opacity (mild cloudiness of lung fields) without well defined borders are often interpreted as passive congestion. These patients usually do not have marked congestive heart failure. Where there has been opportunity to repeat the roentgenogram within a few days there has been noted in a few instances, rapid spread and regression of this haziness, corroborating the transient changes noted clinically in the same patients. There is a remarkable example of a complete subsidence within four days pictured in Poynton and Schlesinger's⁹ text "Advances in the Study of Rheumatism" (1931). The attending physician refused to believe that a pneumonia could so completely subside in such short time.

The Subclinical Pulmonary Involvement of Rheumatic Fever It can safely be said that the majority of moderately ill rheumatic fever patients will not show anything like the striking physical signs of consolidation or of widespread pneumonitis. With increasing evidence of the importance of the pulmonary lesions, however, more complete examination should be attempted and fleeting changes will possibly be detected in many milder cases of rheumatic fever. Moderately impaired breath sounds, slightly to moderately impaired percussion note and possibly a few râles will constitute the "subclinical" lung signs, very brief and not very convincing, yet probably of great importance in the subsequent clinical course of cardio-pulmonary dysfunction. These statements are based on the fact that many patients with negative chest findings in the ordinary routine examination present slight to moderate pneumonitis of the characteristic type at necropsy, in fact, the incidence of pneumonitis in some degree is almost the same as that of myocarditis.

"Inflammatory Collapse"—A Complication of Rheumatic Pneumonia and Pneumonitis The physical signs of consolidation may disappear rapidly in the course of a few days and are not infrequently followed by dullness and impaired or absent breath sounds at the bases. These latter signs may have been present from the beginning. At any rate they persist for many days, even weeks, and are due to pulmonary collapse or atelectasis, usually accompanied by small pleural effusions. This collapse has been noted frequently on the left side and is currently attributed to atelectasis secondary to pericardial effusion. Coombs¹⁰ ascribed it to reflex immobilization of the left diaphragm following pericarditis, we have seen it as a right sided lesion in the absence of pericarditis. Naish suggested that the

constant friction caused by the pulsating heart probably dictated the development of primary inflammation in the adjacent left lung but he rejected the older theory of cardiac pressure with subsequent pulmonary collapse. Possibly a number of factors operate, namely the small to moderate pleural effusions that often accompany the atelectasis, the prolonged confinement to bed with its subsequent diminution of pulmonary function, and probably in some instances, a reflex inhibition of diaphragmatic activity as postulated by Coombs. However, these possible factors do not afford a sufficiently reasonable explanation in the majority of cases. The pleural effusions are usually too small and sometimes absent, as shown at necropsy, and certainly are not to be compared with the massive hydrothorax of chronic congestive heart failure where the atelectasis is less striking in extent.

The most important factor we believe is the pneumonia or pneumonitis *per se*. Basal collapse can be seen not infrequently in conditions other than rheumatic fever, for example, in senile emphysema in conjunction with pleural effusion. (We exclude from consideration the ordinary types of atelectasis—the bronchial obstructive and the compressive.) Evidently the resiliency of the lung tissue is a factor in the development of basal collapse. Following rheumatic pneumonia, there is a distinct loss of the normal elasticity of the parenchyma, a direct result of the “fibrinoid” degeneration of the alveolar walls, with the destruction of the elastic and reticular fibers of the interstitial framework. There is finally a replacement by an interstitial fibrosis in which there is usually a marked regenerative hyperplasia of coarse, irregular and fragmented elastic fibers, the net result of which is not a return to the normal elastic state but a lung tissue that is much firmer, with rubberoid consistency. Where the loss of the elastica has been great and respiratory function temporarily destroyed, the inflammatory congestion marked and air-absorption facilitated, collapse fibrosis is apt to occur. Since the incidence of rheumatic pneumonitis is greatest in the lower lobes, they are the favored site for the development of this lesion. Moreover, those factors which we believe to be of secondary importance, namely, pleural effusion and pericardial effusion will exert their influence largely on the lower lobes. Collapse may involve an entire lobe or a portion of it, and it follows from the foregoing statements that such gross involvement is almost always basal, the collapse, however, may be of lesser proportions, giving rise to small lobular atelectases, we have noted instances of lobular atelectasis in the upper lobes, a location practically immune to the influence of pleural effusion.

The lesion may be termed “inflammatory collapse” in contra-distinction to the mechanical types produced by either external compression or bronchial obstruction. The physical signs of basal dullness and impaired breath sounds often noted even late in convalescence from a severe attack of rheumatic fever, are typical of this lesion. Coarse râles differing from those heard earlier in the state of intra-alveolar consolidation also may persist for

many days or weeks and can be ascribed to a plastic pleural reaction. Whether consolidation necessarily preceded this state or whether severe grades of pneumonitis, short of actual consolidation may equally lead to this same result, cannot be stated with any certainty. Roentgenograms may reveal elevation of the diaphragm on one or both sides, with or without small pleural effusions. "Hypoventilation" of the lungs due to elevation of the diaphragm is a diagnosis occasionally made by the roentgenologist.

It is questionable whether the function of such collapsed lung tissue can ever return to normal. In a case recently seen at necropsy, the lower right lobe was still considerably shrunk in size two months after the diagnosis of rheumatic pneumonitis had been made. We have no later direct observations on this point, but inasmuch as the interstitial fibrosis that follows rheumatic pneumonitis will in all likelihood be exaggerated in areas that were collapsed, it is reasonable to assume that respiratory function will remain impaired in spite of re-aeration. It is believed that respiratory exchange is diminished in areas of interstitial pulmonary fibrosis (the state known in the German literature as "pneumonose")^{11, 12, 13}

*The Probable Relationship of Ewart's Sign (of Pericardial Effusion)*¹⁴ to Rheumatic Pneumonia and Inflammatory Collapse.* Bronchial breathing suggestive of consolidation is not infrequently found at the angle of the left scapula, due it is claimed to an atelectasis secondary to pericardial effusion rather than to pneumonia. This is an old observation known as Ewart's sign. It is significant that while this sign is encountered in the great majority of instances in young patients with rheumatic fever, much greater effusions noted occasionally with tuberculous pericarditis do not produce identical signs of "false" consolidation.

We have had ample opportunity to study sections from atelectatic left lungs in acute rheumatic fever with pericarditis. Such sections show a pneumonitis, a definite inflammatory reaction similar to the pneumonia or pneumonitis encountered in the right lobe, of the same patient if such a localization has developed, or in the right lung of other patients. The tendency to collapse in rheumatic pneumonitis, described in earlier paragraphs as due to the impaired elasticity and destruction of normal interstitial connective tissue, is the probable basis of Ewart's sign. Lung tissue so involved is probably vulnerable to pressure from any direction, if this assumption is correct, then pressure exerted by pericardial effusion merely hastens and accentuates the signs of a pulmonary inflammation already present.

SUMMARY

Pulmonary consolidation constituting a true pneumonia is often seen in severe cases of rheumatic fever, a lesser degree of lung involvement, not

* Ewart listed ten signs of pericardial effusion, of which the eighth dealt with "the posterior pericardial patch of dullness," a sign previously noted by Bamberger (1867), Pins (1889), and Samson (1892), the tenth was the "posterior pericardial patch of tubular breathing and egophony" which has been combined by usage with the eighth sign as Ewart's sign of pericardial effusion.

actual consolidation, preferably termed "pneumonitis," is frequently encountered. These changes are not secondary complications but an integral part of the disease. The clinical manifestations are often overlooked because of the transient character of the consolidations and the inability to examine the bases of the lungs of patients wracked with arthritic pain.

In most patients with rheumatic pneumonia there is a characteristic disproportion between symptoms and physical signs, the latter being the most striking. Respiratory distress is comparatively slight but becomes marked when pulmonary involvement is almost complete. The acute inflammation is followed in some cases by a characteristic "inflammatory collapse," usually basal, the main factors appear to be a loss of elasticity, air-absorption, and subsequent contracture due to interstitial pneumonitis.

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THE NECESSITY OF CERTAIN CRITERIA FOR THE DIAGNOSIS AND CURE OF RHEUMATOID ARTHRITIS*

By RUSSELL L. CECIL, M.D., F.A.C.P., *New York, N. Y.*

PERHAPS the most important problem which confronts a young medical organization such as the American Rheumatism Association is the proper orientation of the Society in the field which it proposes to cover. This question has already been attacked in part by this group. In the first place we decided that we would not confine ourselves strictly to the matter of arthritis, but would cover the whole field of rheumatism, including rheumatic fever. Our next task is to attack the problem of nomenclature, and what a difficult problem it is! The English have already made a brave effort in this direction, and their achievements are covered in the report of the Subcommittee on Nomenclature of the National Rheumatism Committee, which was appointed by the Royal College of Physicians. In our own country the American Heart Society has set us a fine example in their classification and nomenclature of diseases of the heart. This subject is much too large to be covered by a president's address. Today I simply wish to point out the necessity of establishing certain criteria for the identification of rheumatoid arthritis, a disease which might well be called the key-stone of our problem. I shall also say something concerning the criteria essential for the pronouncement of cure in this disease.

Rheumatoid arthritis is one of the great diseases of medicine. With tuberculosis and syphilis it constitutes the great triad of chronic granulomatous infections prevalent in our climate. This fact in itself would help to explain the rapidly growing interest in chronic arthritis, and in rheumatoid arthritis in particular. But there is an even stronger reason for the increasing interest in rheumatoid arthritis. It is one of the few remaining unsolved problems in the field of infectious diseases. To be sure, there are many things we do not understand about tuberculosis, syphilis, pneumonia, and other infectious diseases, but at least we know their causes. In the case of rheumatoid arthritis we are still debating the etiology, and much work remains to be done before this problem can be settled. Etiology, however, is only one of the many problems connected with rheumatoid arthritis. We must learn more about the influence of heredity and other predisposing factors such as climate, constitution, malnutrition, avitaminosis, etc. And finally, we must learn how to treat the disease successfully. We might say that rheumatoid arthritis today stands in the same position that tuberculosis occupied 60 or 70 years ago before Robert Koch discovered the tubercle bacillus. Rheumatoid arthritis is waiting for its Robert Koch, and I for

* President's Address, read before the Fourth Annual Meeting of the American Rheumatism Association at Atlantic City, New Jersey, June 7, 1937. Received for publication July 9, 1937.

one believe that within the next 10 years he will probably make his appearance

Before taking up in detail the criteria which are necessary for the diagnosis of rheumatoid arthritis, let us review briefly the classification of the British National Committee¹ Under the heading of "rheumatoid arthritis" we find the following subdivisions

(1) Rheumatoid arthritis with associated factors Under this heading are placed metastatic or focal arthritis, including so-called multiple infectious arthritis, in other words, the rheumatoid type of arthritis closely associated clinically with focal infection Under the same heading the English classifiers place rheumatoid arthritis associated with the disordered metabolism of the menopause—a rather dubious effort to tie up the disease with another well recognized pathologic condition

(2) Rheumatoid arthritis with no known associated factors Under this heading the British include the classic type of rheumatoid arthritis as it is seen in women during the child-bearing period I might add that it is also seen at this time of life in men even though they do not bear children Under this heading the British also include Still's disease, or the rheumatoid arthritis of children The British Committee then draw a "deadly parallel" between rheumatoid arthritis with known associated factors and rheumatoid arthritis with no known associated factors, and attempt to make a clinical distinction between the two groups The differentiation occupies more than four pages of text, the reading of which does not convince one that such a differentiation is feasible or desirable About the only real difference between the two groups is that the first group is associated with definite focal infection whereas in the second group no focus of infection is demonstrable, but we all know how frequently foci of infection can be missed, even after the most careful study, and we also know that on the other hand teeth, tonsils, and sinuses are often blamed for crimes which they did not commit Therefore, it seems to me that this differentiation of rheumatoid arthritis into two groups, while intriguing, is not justified So far as we have been able to make out from our studies, both types present the same pathological and clinical manifestations, and the immune responses are the same for both groups For the time being, therefore, I suggest that in America we continue to look upon rheumatoid arthritis as a single disease and that we attempt to establish certain criteria for its identification

In discussing the necessary criteria for the diagnosis of rheumatoid arthritis, we may divide them into pathological, clinical, radiological, and serological findings

1 The pathological criteria are quite definite, but unfortunately are not obtainable except by means of a biopsy In a certain number of cases a synovectomy may be indicated and tissue becomes available for microscopic study The gross pathology of the joint is not sufficiently characteristic¹⁴ might be simulated by some other form of joint infection, particularly the

gonococcal joint Microscopically, a vascular granulation tissue containing collections of lymphoid cells which often resemble true lymphoid follicles, presents a picture which in my experience, one never sees except in rheumatoid arthritis If a subcutaneous nodule presents itself it can readily be removed, and again microscopic study reveals the characteristic histologic changes so well described by numerous pathologists As pointed out by Dawson,² these changes do not differ widely from those observed in the subcutaneous nodules of rheumatic fever However, the nodules of rheumatoid arthritis are usually larger than those of rheumatic fever, and not so likely to appear and disappear

2 Clinical Criteria The clinical criteria of rheumatoid arthritis are perhaps the most important of all, and of these, the most characteristic is the fusiform finger Periarticular swelling is of course a feature of any form of joint infection, but the peculiar, doughy enlargement of the proximal interphalangeal joints of the fingers is the outstanding badge of rheumatoid arthritis The fusiform finger usually appears early in the disease and may persist for years Eventually however, as the disease passes into the inactive stage, the swelling in large part disappears and is replaced by ankylosis and deformity Closely associated with the fusiform swelling of the fingers, and almost as frequent is a swelling of several knuckles, which when accompanied by atrophy of the interosseal muscles, gives the hand its characteristic appearance

The second clinical criterion is the multiplicity of joints involved The disease is still often spoken of as chronic multiple arthritis It is indeed rare to see only one joint affected I recall in my practice one young woman who showed a fusiform swelling of the index finger of the left hand She was a slender under-nourished girl of 23 years, and I fully expected to see the disease extend eventually to other joints However, no other joints were ever involved during the two years or more that she was under my observation During that time the swelling of the finger remained practically unchanged I was suspicious of tuberculosis in this case, but it could not be proved by roentgen-ray or other diagnostic methods In discussing the characteristic lesions of the hands and fingers in this disease, I am tempted to include the frequent involvement of the wrists and particularly their early tendency to ankylosis However, this could hardly be looked upon as one of the essential criteria, neither could the vasomotor disturbances of the hands and feet, though I always expect the rheumatoid arthritic to greet me with the cold, clammy hand so typical of the disease The wasting of the muscles and the atrophy of the skin and subcutaneous tissues are seen in other forms of infectious arthritis as well as in the rheumatoid type There are other favorite sites of rheumatoid manifestation, particularly the knees, feet elbows and cervical spine I have never been able to understand why the hips and the toes so frequently escape involvement

I have already referred to the highly characteristic subcutaneous nodule. When present, it is almost pathognomonic of the disease, but unfortunately it occurs in only 4 or 5 per cent of cases. Certain other clinical phenomena, such as iritis, psoriasis and the various forms of erythema, are frequently associated with rheumatoid arthritis, but could in no sense be considered as criteria of the disease.

Should the physician ever make a diagnosis of rheumatoid arthritis in the entire absence of swelling or deformity of the joints? Only rarely would such a diagnosis be justified, though one might be strongly suspicious of what I often call the pre-arthritic stage of the disease.

3 Radiographic Criteria The roentgen-ray appearance of the bones and joints in rheumatoid arthritis is highly characteristic, so much so that it is usually possible to make a diagnosis of the disease by this means alone. In the very early stages there are no typical manifestations. Soon, however, the roentgen-rays begin to show the characteristic decalcification of the bones and the soft tissue swelling. As the disease progresses there is narrowing of the inter-articular space due to thinning of the cartilage, and blurring of the whole joint architecture. Several writers have stressed the peculiar punched-out areas, which are a prominent feature of rheumatoid arthritis, and occur just as frequently in this disease as in gout. In the latter disease, however, the punched-out areas are much larger than those in rheumatoid arthritis. In the final stages of rheumatoid arthritis the joint surfaces may become fused through fibrous or bony ankylosis, and in deformed joints there may be subluxation or dislocation. In the late stages hypertrophic changes may be observed, but this should not lead to confusion of the disease with osteo-arthritis.

Can a definite diagnosis of rheumatoid arthritis be made from the roentgen-ray pictures alone? In very early cases, no. In well established cases, yes, in a high percentage of cases. Occasionally, a gonococcal arthritis might be a source of error, but the anamnesia and other clinical data would prevent a mistake in diagnosis.

4 Serological Criteria The most characteristic blood change in rheumatoid arthritis is the agglutination of the *Streptococcus hemolyticus* by the patient's serum, usually in high dilutions. This test is positive in a large proportion of cases, the actual percentage of positive reactions depending on the duration of the disease. In early cases the presence of agglutinins is not so conspicuous a finding, but in the original report which the writer made with Nicholls and Stainsby in 1931,³ we obtained a positive agglutination reaction in 97 per cent of 153 cases of well established rheumatoid arthritis. Dawson, Olmstead and Boots⁴ demonstrated the presence of streptococcal agglutinins in 67 per cent of their series, Blair and Hallman,⁵ in 85 per cent of their patients.

We may conclude then that while a positive streptococcal agglutination reaction is present in a high percentage of cases of rheumatoid arthritis, it

is not invariably present. It may be said, however, that a positive agglutination reaction is strongly confirmatory of rheumatoid arthritis and should be looked upon as one of the important diagnostic criteria.

Other immunological phenomena have been noted in the serums of patients with rheumatoid arthritis. I refer to the ability of rheumatoid sera to precipitate the various group specific fractions of the *Streptococcus hemolyticus* and to the presence of anti-streptolysin in the sera of some patients with this disease. Neither of these antibodies, however, is so consistently present as are the agglutinins. For this reason they could not be looked upon as important criteria in the diagnosis of the disease.

Another reaction of considerable importance is the sedimentation rate of the red blood cells. The sedimentation rate shows sharp acceleration in practically 100 per cent of cases of rheumatoid arthritis during the active stage of the disease. This test of course does not differentiate rheumatoid arthritis from other forms of infectious arthritis. However, a rapid sedimentation rate is an important feature of the disease.

A moderate grade of leukocytosis, with some increase in the percentage of immature cells, is seen in a good many cases, but is not a constant enough finding to be dependable. The same is true of the secondary anemia which so frequently accompanies the disease.

Summarizing then, we may say that a patient with rheumatoid arthritis should present the picture of a chronic progressive multiple arthritis characterized in its earlier phases by soft tissue swelling, and in its later stages by some ankylosis and deformity. Implication of the interphalangeal, metacarpophalangeal and wrist joints is especially characteristic. The synovial membrane and the subcutaneous nodules, when present, show specific histological changes. The radiographic evidence is quite typical, and the patient's serum in a large majority of cases will induce an agglutination of the *streptococcus hemolyticus*. A rapid sedimentation rate of the red blood cells is highly characteristic, but is seen in other forms of infectious arthritis as well.

Let us now turn our attention for a few moments to the question of criteria for determining the cure of rheumatoid arthritis. Such criteria are obviously needed and should serve as a guide to any of our members who report on the effects of this or that remedy in the treatment of the disease. There are entirely too many articles being written on the treatment of rheumatoid arthritis. Most of them fail to take into account the natural tendency of the disease to remissions and exacerbations, and the writers are too content to state that such and such a percentage of patients were "improved" by the treatment under consideration. Personally I will not be permanently satisfied with any remedy for arthritis which merely improves the patient. We must strive for a *cure*, something that will give the patient complete and permanent relief from the disease. When should we be willing to pronounce the rheumatoid patient cured? I should say that the first

requirement would be clinical cure evidenced by freedom from pain and swelling of the joints and partial or complete return of joint function. In addition to freedom from joint symptoms the patient should feel well and should be entirely relieved of the exhaustion and fatigability which so frequently accompany the disease. At this point, however, we must make certain qualifications in our criteria. It is true that cure in an early case frees the patient from practically all earmarks of the disease. In those comparatively rare instances, however, where a well-established arthritic recovers from the disease a number of scars may remain. The patient returns to normal health and the joints are free of swelling and pain, but there may be some residual enlargement. Ankylosis and deformity may persist in certain joints, but the patient does not mind this when he feels so well in all other respects.

In a cured case the sedimentation rate of the red cells should return to normal, and the specific agglutinins for the hemolytic streptococcus should disappear from the patient's serum. The leukocyte count returns to normal, and the secondary anemia is replaced by a normal blood count.

Roentgen-ray pictures may reveal certain residual damage to several of the joints, but in early cases radiographs may show little or no evidence of permanent joint damage.

The patient should not be looked upon as a cure until he has remained free of symptoms for at least one to two years.

Would it not be worth while for this Society to appoint a committee whose duty it could be to set up certain criteria for the diagnosis and cure of rheumatoid arthritis? The acceptance of such criteria by the members of this group would, in my opinion, greatly advance the cause of efficient therapy. When the curative effects of the numerous types of therapy were analyzed with such criteria in mind, perhaps fewer but more intelligible contributions to the literature of rheumatism treatment would be made.

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METABOLIC STUDIES IN A MAN WHO LIVED FOR YEARS ON A MINIMUM PROTEIN DIET*

By FR STRIECK, Ph D , M D , *Wurzburg, Germany*

I have on several occasions had the opportunity of cooperating in making interesting studies of persons who voluntarily carried out with great care and devotion a one-sided extreme diet. Such were the final studies by Dr E F DuBois,¹ upon Dr V Stefansson and K Andersen, both of whom had lived for a long time exclusively upon meat and fat and the internal organs of butchered animals. We were able also in 1933 and later to carry out observations on a well known nutritional physiologist, Dr C Rose, who for 15 years investigated the question of the minimum protein requirement, the protein optimum, the biological value of single varieties of protein and other related problems.

In the study of problems of nutrition, protein, the most important and indispensable of foodstuffs, has been the repeated object of investigation. The literature concerning this substance is almost too great for review, and many questions here seem to be still unexplained. It would be far beyond the limits of this paper to present even a partially comprehensive survey of this problem. The collected literature may be found in the papers of Heupke,² Hindhede, and Susskind.³ I should like to limit myself to a few questions which I have studied in association with Dr C Rose in the last few years, namely, the question of efficiency on a protein poor diet, the total metabolism at the borderline of minimum protein requirement, and the specific dynamic protein effect after feeding varieties of protein of different biological value in varying amounts.

Since there is a want of clearness in the literature concerning the minimum protein requirement, I should like first to briefly define protein minimum. We understand by the minimal nitrogen excretion, which was termed by Rubner the wear and tear quota, the smallest or lowest nitrogen excretion values in an individual on a protein free diet. The physiological protein minimum is found when the minimal nitrogen balance is reached, i e , when output and intake balance one another. The physiological protein minimum is independent of the kind of protein, the state of nutrition or other factors. It is necessary in the technic of the investigation, not only that an analysis be made of the excretions (feces and urine) and of the perspiration and secretions of the skin, but also that there be an exact determination of the composition of the diet which is fed. Differences from table values by as much as 50 per cent may occur. Months or years of prolonged series of

* Received for publication June 23, 1937

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diets with similar foodstuffs presuppose, if the conclusions are to be clear and unequivocal, a continuous analysis of the single basic foods, such as potatoes, milk, bread, etc. We have carried out these analyses.

Factors which influence the minimal nitrogen excretion are, aside from those already mentioned, the compatibility of the usually very onesidedly constructed diet, vitamins, the amount of fluid, the state of nutrition, the time of life, the acid base balance, and the biological value (quantivalence) of the single varieties of protein.

The very question of the acid base economy is still a much debated question, in connection with which Rose, R. Berg and others have developed a special point of view. The richness in base of the diet and the previous output of acid are of decisive importance in the question of the minimal protein requirement. In careful metabolic studies Rose has recently tested again the relation between minimum protein requirement and the base content of human food. In a preliminary period, with a protein intake of 28.17 gm daily and the addition of basic salt, he found a nitrogen storage of 0.60 gm. The urine was alkaline at this time. In the main period he left out the basic salt, keeping the amount of protein the same, with an exactly similar diet. The urine became acid and the loss of nitrogen amounted to 0.44 gm. If he then added basic substances, a storage of 0.155 gm of nitrogen occurred during the after period. The total calories were 2651 in 24 hours. Rose attributes the negative nitrogen balance on the same nitrogen intake during the main period to the lack of an excess of base. The less the formation of ammonia, the smaller is the wear and tear quota. Thomas had already found earlier that the value for the smallest protein requirement cannot be kept constant with bread and meat, if sufficient basic substances are not simultaneously present. This phenomenon is due to the marked formation of ammonia.

It has already been mentioned that the biological value of individual protein substances differs, that is, the capacity of individual protein substances to attain a minimal nitrogen balance, differs. With milk, Rose achieved this with 20.5 gm protein, in the case of a potato diet, with 26.5 gm, with an exclusive banana diet it required 46 gm.

So far as I know, there have never been any studies anywhere which were carried out on a human being who existed for 15 years on an average daily protein intake of 38 to 40 gm, who during an experimental period lasting for years took daily only 26 gm, and who at times, during periods of negative balance, took only 20 gm of protein. Neither Hindhede nor Chittenden, Thomas, Rubner, or Lusk has been able to carry through such series of investigations. The unique character of these experimental conditions led us to report the results of efficiency tests in this subject.

Rose carried out extraordinary performance tests in 1931 together with his friend Dr. Schmitt, a Swiss physician of Thun, who for 25 months likewise ate only about 30 to 40 gm of vegetable protein with an adequate

caloric intake Dr Rose (D R), at that time almost 70 years of age, climbed several mountains over 4000 meters in height Dr Schmitt (D Sch), who at that time was 35 years of age, climbed in 22 ascents, for example, Monte Rosa (4500 m), the Matterhorn (4500 m), the Weiss-horn, Grosse Viescherhorn and other mountains without disturbance in his efficiency, signs of great fatigue or any indication of exhaustion in spite of the small intake of protein

Because of its general biological significance, I should like to mention in addition the negative balance experiments which Dr Rose carried out on himself We studied him at the end of this period The total protein intake was 23 gm , the minimum requirement as determined from the preliminary studies of years, 28 gm There was no vitamin lack The amount of calories ingested was adequate There slowly developed an increasing loss of appetite, diminution of interest in work and a feeling of depression The experiment had to be interrupted because of these complaints A second period of equal duration had to be interrupted because the complaints grew intolerable

The question as to whether during a state of minimal nitrogen equilibrium, the most strenuous bodily exertion results in a greater output of nitrogen, i e , an increased destruction of protein, in a healthy individual, can be answered in the negative as a result of Rose's studies in Switzerland in connection with his mountain climbing, and our own experiments with the brake ergometer and marching exercises (Marschleistungen) During mountain climbing Rose had a positive balance with 24 to 29 gm protein in his diet and excellent physical efficiency In our clinic D R showed an average nitrogen output of 3.9 gm daily He remained in nitrogen balance For days at a time he worked at the brake ergometer to the point of exhaustion, without developing a negative balance Further he walked 50 km on a hot sunny afternoon in mountainous country without being exhausted or showing an increased nitrogen secretion

It seemed of interest to us to test the oxygen consumption during and after work We made the investigation with Krogh's brake ergometer, changing the load and the speed The same tests were carried out on D Sch by Brumann We were able thus to determine that the oxygen consumption is less per unit of time, but that the period of recovery (corresponding to the oxygen debt) is nevertheless distinctly prolonged We have made approximately 20 similar tests in the past three years, always with similar results

In 1933 and 1935 we studied the basal metabolism after a protein poor period and after meat All the following studies of the respiratory gas exchange were made with the Grafe Universal respiratory apparatus, the gas analyses being carried out with the Haldane Carpenter apparatus

The values are presented in table 1 The amount of rise was calculated in accordance with the Harris-Benedict tables The average elevation both

TABLE I
Basal Metabolism Figures

Date	Calories	R Q	%
3/13/33	1633	0.81	+16
3/15/33	1636	0.82	+17
1/3/35	1567	0.84	+18
1/4/35	1478	0.82	+11
1/6/35	1489	0.86	+12
1/8/35	1549	0.83	+16

in 1933 and 1935 is about 15 per cent. The values are not comparable with standard figures since D. R. is an unusually energetic, muscular, high spirited man who, from the biological viewpoint, is not as old as would be assumed from his actual age. On each occasion we gave D. R. a careful physical examination. The findings, including roentgen studies, showed no indication of any demonstrable disturbance or wear and tear in his internal organs. There was complete lack of any definite indication of arteriosclerosis. While in the case of D. Sch. the basal metabolism was depressed by about 10 to 15 per cent during the protein poor period of his test, I found a measureable increase in the case of D. R. I prefer not to consider this a true increase in the total combustion but, for the reasons mentioned above, believe these values to represent his normal figures.

The studies of specific dynamic action which, so far as I am aware, have never previously been carried out on a man of this age under similar nutritional conditions, gave peculiar results in 1933. We were interested in the question of the specific dynamic effect of the protein poor diet. The result surprised us in that the increase in total combustion was extraordinarily high and still remained considerably elevated even after six hours. This was confirmed in a control test.

TABLE II
Specific Dynamic Effect after Potatoes (3/14/33)

Time	Calories	R Q	%	
1 hour	2204	0.79	+35	350 gm potatoes, 100 gm butter, 20 gm sugar. Total calories 1226.3, P 8.5 gm, F 85.8 gm, C 93.56 gm
2 hours	1958	0.83	+19	
3 hours	2045	0.88	+25	
4 hours	1810	0.81	+11	
5 hours	2575	0.89	+58	
6 hours	2570	0.89	+57	

The elevation of metabolism was already perceptible after one hour, and after six hours was still 57 per cent. A few days later we then gave a 10-fold greater quantity of protein in the form of meat (table 3). The maximal increase occurred in the first hour and amounted to 22 per cent.

TABLE III
Specific Dynamic Effect after Meat (3/17/33)

Time	Calories	R Q	%	400 gm meat, 73 gm butter Total calories 1194, P 80.5 gm
1 hour	1986	0.83	+22	
2 hours	1866	0.87	+14	
3 hours	1839	0.71	+13	
4 hours	1940	0.72	+19	
5 hours	1809	0.81	+11	
6 hours	1955	0.82	+20	

After a further three day meat diet we determined the specific dynamic effect again and found a very delayed rise, which began only after four hours. The highest value was attained after $5\frac{1}{2}$ hours amounting to +26 per cent (table 4)

TABLE IV
Specific Dynamic Effect after Meat (3/20/33)

Immediate	- 0.9%	400 gm meat, 73 gm butter Total calories 1194, Protein 80.5 gm
$\frac{1}{2}$ hour	- 1.3%	
1 hour	+ 0.2%	
$1\frac{1}{2}$ hours	- 1.3%	
2 hours	+ 9.0%	
$2\frac{1}{2}$ hours	+ 3.5%	
3 hours	+ 6.7%	
$3\frac{1}{2}$ hours	+ 2.3%	
4 hours	+16.5%	
$4\frac{1}{2}$ hours	+11.1%	
$5\frac{1}{2}$ hours	+26.1%	
6 hours	+ 9.4%	
$6\frac{1}{2}$ hours	+17.3%	
7 hours	+21.7%	
$7\frac{1}{2}$ hours	+17.5%	
8 hours	+19.3%	
$8\frac{1}{2}$ hours	+ 6.7%	
9 hours	+ 7.0%	
$9\frac{1}{2}$ hours	+10.4%	

After two years of a protein poor diet, conditions were somewhat different. We arranged, instead of a test of short duration, a period of study lasting 24 hours. The apparatus made it possible to study an individual all day and all night and permitted taking food during the same period. On this occasion the total metabolism rose during the afternoon by 37 per cent. It is to be noted that a small percentage of the increase must be attributed to muscular exertion, as D. R. did not lie quietly at rest. During the night the metabolism fell 13 per cent (table 5). After six days we again studied the specific dynamic effect after meat. The increase here was again about the same as before (table 6). To what may now be attributed the altered behavior of the metabolism?

TABLE V
24 Hour Test (1/5/35)

Time	Calories	R Q	%	Diet
8 15 a m -12 43 p m	1838	0 81	+24	8 15 a m coffee 400 gm , cream 20 gm , sugar 20 gm
12 48 p m - 5 53 p m	1875	0 83	+27	12 15 p m potato 300 gm , tomatoes 100 gm , butter 100 gm
5 58 p m -10 46 p m	2020	0 84	+37	3 15 p m coffee 400 gm , cream 20 gm , sugar 20 gm
2 52 a m - 6 11 a m	1282	0 86	-13	
6 18 a m - 8 51 a m	1489	0 86	+ 1	6 15 p m curdled milk 400 gm , crackers 50 gm , butter 50 gm , sugar 30 gm

TABLE VI
Specific Dynamic Effect after Meat (1/11/35)

Time	Calories	R Q	%	
1 hour	1854	0 85	+25	
2 hours	1918	0 79	+30	
3 hours	1838	0 80	+24	
4 hours	1979	0 76	+34	
5 hours	1598	0 83	+ 8	
6 hours	1898	0 86	+28	
				Meat 400 gm , butter fat 65 gm Total calories 1067, P 88 gm , F 77 gm , C 3 gm

No assured interpretation can be given, as long as the nature of specific dynamic action itself is not clear. For the present we must limit ourselves to reporting the observed facts.

During the course of the protein minimum experiment we studied the loss of nitrogen through the skin. We determined the amount of protein given off by means of the skin and perspiration over an experimental period of five days during which unmeasurable losses were avoided so far as possible. The method was the same as that used by Rubner. I give our results, inasmuch as these experiments have only rarely been carried out and since in accurate equilibrium experiments these values must be taken into consideration. During the five day experimental period there were excreted through the skin 0.483 gm of nitrogen. We studied the blood chemistry in the case of D. R. during the 1935 experimental period both before and after the meat diet. The blood sugar was 89 mg per cent before the meat diet, and 92 mg per cent after it was begun. The non-protein nitrogen was normal, 39 mg per cent, blood chlorides were 514 mg per cent, blood uric acid 3.32 mg per cent. Similar values were obtained during both meat and vegetable diets.

From the studies on D. R. it may be concluded that it is possible to live for years on a one-sided diet which includes protein foods of high biologic value such as potatoes and milk, which has an adequate vitamin and caloric

content, and an amount of protein which is extraordinarily small as compared to the general average consumption and by Voit's and Rubner's figures. In spite of this, vigorous physical activity was possible without any demonstrable hurt and without a negative balance during the period of exertion. D. R. puts great faith in potatoes to cover his protein requirement. He has succeeded in cultivating a potato which is unusually rich in protein and palatable, the protein content of which amounts to more than 2 to 3 per cent. It is no doubt possible to live for a long period, without injury to health, on a low protein diet containing approximately 30 gm of protein. The positive balance is immediately changed to a negative balance if the physiological discharge of vital functions is disturbed by illness. A harmless illness occasions an increased protein consumption under these dietary conditions, thereby bringing about a negative balance. D. R. has often confirmed this. Therefore, a surplus of at least 10 to 15 gm is necessary for the safety of the organism. But other observations also give rise to the presumption that demands are laid upon the vital reserves by such a nutritional program. Towards the end of the two year series of experiments D. Sch. observed that he experienced an increased need of rest, his pulse became slower and the axillary temperature rose. Susskind's investigations cannot be subjected to critical study since they were carried out with a protein which was not biologically of high quality, with insufficient vitamin feeding and without accurate analyses. It may be assumed that he lived for a long time in a state of negative balance and that the marked disturbances and resultant collapse are thus to be explained.

If we compare the experiments of Stefansson and Andersen with those of Rose, representing two extremes, we realize how adaptable the human organism is and how multifarious must be its system of safeguards. The meat and fat eaters showed a normal behavior in every respect—total metabolism, protein metabolism, kidney function, efficiency, blood synthesis—in short, all measureable functions except the calcium metabolism were undisturbed. In the case of Rose too all body functions were normal. Physical efficiency was indeed astonishingly good.

Both forms of diet are out of the question so far as actual practical use is concerned. Strong will power and a high degree of fanaticism are necessary in order to follow so one-sided a diet for a long period of time. That it is possible is shown by these investigations.

SUMMARY

Metabolism studies were carried out on a 70 year old, healthy man who for years had been on a diet containing about 30 gm of protein daily. The basal metabolism was elevated 15 per cent in comparison with the Harris-Benedict figures. The specific dynamic effect of protein was higher after vegetable protein than after meat protein. The blood chemistry was un-

changed Physical efficiency was excellent After the most severe bodily labor there was no increased excretion of nitrogen The nitrogen output through the skin amounted to 0.483 gm over a five day period

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A PHARMACOLOGIC STUDY OF THE MECHANISM OF GOUT*

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DR PRATT'S long interest in and contributions to the subject of gout make it a particularly appropriate subject for his birthday volume. It is especially fitting that these observations be reported here since they had their inception in a research the author was privileged to share with Dr Pratt¹

In these experiments we concluded that the action of cinchophen on uric acid excretion was exerted through the central nervous system. At that time methods for testing this suggestion were wanting. With the development of new methods it became possible to test this hypothesis in the experimental animal. In the last three years I have shown that the above concept is correct and that the effects of cinchophen on uric acid excretion do, in fact, depend upon an intact renal nerve supply. This lends support to the idea that the syndrome of gout is associated with changes in the function of the autonomic nervous system, through a mechanism similar to the one concerned in the action of cinchophen on the uric acid excretion.

Thannhauser² has long maintained that the mechanism of uric acid retention was primarily a renal dysfunction, probably concerned with the nervous connections of the kidney. While the frequent association of nephropathy with gout has been adequately stressed, the numbers of patients without evidence of renal lesions have militated against the whole-hearted acceptance of the renal theory³. Thannhauser based his idea of the effects of the renal nervous mechanism on the experiments of Ellinger and Hirt⁴. These experiments, however, showed relatively small differences and were acute experiments with all the difficulties and extraneous factors that acute experiments under anesthesia entail. Although the variations in excretion that they report seem very small, they evidently felt them to be sufficiently constant and consistent to draw the conclusion that the renal nerve supply affected renal cellular activity and that these nerves, therefore, were "secretory nerves" in addition to being "vasomotor nerves". Marshall and Kolls⁵ working with anesthetized dogs were unable to confirm their results and concluded that these nerves had only a vasomotor function.

In 1931, Pratt and I¹ concluded that the action of cinchophen on uric acid excretion was through the central nervous system. This conclusion was arrived at by a study of the uric acid excretion of normal human individuals and a consideration of the literature. Since that time studies on

* Received for publication August 5, 1937

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the action of cinchophen have concerned themselves primarily with the toxic effect on the liver and have not thrown any new light on the mechanism of its action on the uric acid excretion. Since the end product of nucleic acid metabolism in the dog is chiefly allantoin with only small amounts of uric acid, it was only with the introduction of a rapid, accurate colorimetric method for the determination of allantoin⁶ that it became possible to undertake a series of crucial experiments as to whether the above-mentioned hypothesis concerning the action of cinchophen was correct. In brief, if cinchophen acted on the end-product of nucleic acid metabolism as a part of its action on the central nervous system, it would be a simple matter to prove or disprove this point by giving the drug to animals whose kidneys had been disconnected from the central nervous system. Such experiments were undertaken. Fortunately the study of the uric acid excretion was made in addition to the allantoin excretion. It was found that the effect of cinchophen on the uric acid excretion was profoundly modified by denervation of the kidneys whereas the effect on allantoin excretion was only slightly changed.⁷ When cinchophen is given to the dog an increase in allantoin and uric acid excretion occurs without an increase in urinary volume. This seems to support Thannhauser's idea that the drug acts chiefly by increasing the concentration of uric acid in the urine. When, however, the drug is given to a dog with denervated kidneys, instead of causing an increase in uric acid excretion, a decrease occurs despite the fact that the volume of urine is always greater in the dog with denervated kidneys.⁸ It is evident from this that the action of cinchophen is not primarily concerned with concentration. Since the uric acid in the urine of a normal dog may be entirely exogenous, it seemed desirable to try the effects of the drug on a Dalmation hound which as a constitutional anomaly is unable to oxidize all uric acid into allantoin, occupying a position in this respect midway between other dogs and man. A chart of one of our experiments on a pure-bred Dalmation dog is shown herewith (figure 1). It will be seen that the effect of cinchophen on the excretion of uric acid is reversed as is the case in the normal dog. This reversal becomes progressively less as time goes on, and as regeneration of the renal nerves is completed the original reaction is restored. This experiment disposes effectively of the contention that there may be a difference in the handling of exogenous and endogenous uric acid, at least as far as the kidney is concerned. While these experiments show conclusively that the action of cinchophen on uric acid excretion is mediated through the nervous system, the increase in allantoin excretion was not explained. In order to understand this mechanism better it was decided to try to separate the sympathetic from the parasympathetic supply of the kidney by pharmacological means since this cannot be done satisfactorily by surgical methods.

To accomplish this two drugs are available. Ergotamine and atropine in adequate doses will block sympathetic and parasympathetic impulses re-

spectively It must be remembered that the latter connections of the kidney are partly through the celiac ganglion though some direct connections have been described ^{4,9} It seems likely from Feldberg's work,¹⁰ that preganglionic fibers are cholinergic and may be affected by atropine even though the impulses they carry terminate in so-called adrenergic postganglionic fibers Consequently, complete separation of the two parts of the sympathetic system is not possible and overlapping of results may occur However, by

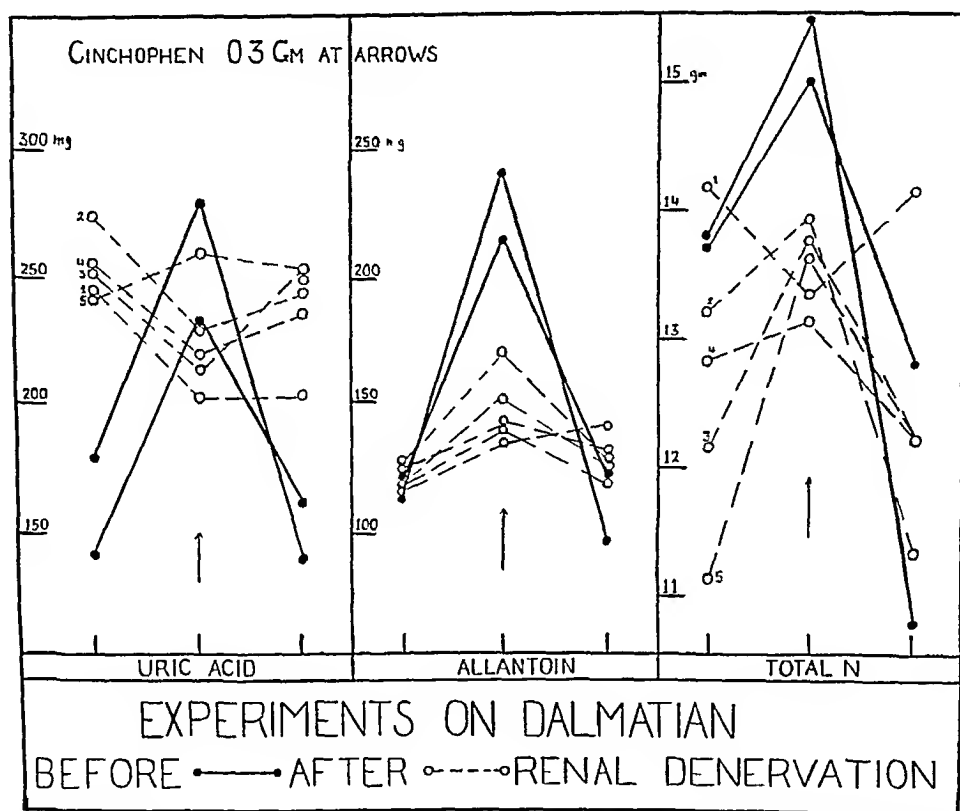


FIG 1 Each point on abscissa represents the average 24 hour excretion of a three day period The figures opposite the dotted line curves indicate the order of the experiments after the kidneys had been surgically denervated

pharmacologic means plus the application of anatomic facts, the two systems can usually be separated by inference at least

The results of experiments ¹¹ employing either ergotamine or atropine simultaneously with cinchophen are compared with the effects of complete renal denervation in the accompanying table A consideration of these results indicates that the effect of cinchophen on allantoin excretion is mediated through the parasympathetic whereas that on uric acid excretion is mediated by the true sympathetic It becomes clear from this that uric acid excretion may be modified by the autonomic nervous system

If this be true, ergotamine in appropriate doses might affect uric acid excretion under certain conditions. In the experiments cited above ergotamine alone had no significant effect on either uric acid or allantoin excretion but did produce a diuresis. The same dose was able to modify the effect of cinchophen on uric acid excretion. Its action therefore is such that it may modify abnormal stimuli to uric acid excretion through the sympathetic. Any effect on uric acid excretion after the exhibition of this drug suggests the existence of abnormal sympathetic impulses through the renal nerves. This possibility had been foreseen many years ago by Thannhauser, and Harpuder¹² concluded that there was some diminution in uric acid excretion in normal individuals after the exhibition of ergotamine. However, his figures do not show highly significant changes. In a personal communication, Thannhauser has stated that he has always seen a diminu-

TABLE I

A summary of results obtained in the experimental studies of the uricosuric effects of cinchophen. In each case the comment indicates the results on this action when the indicated drug was given simultaneously with cinchophen.

Action of Cinchophen		
Modified by	On Excretion of	
	Uric Acid	Allantoin
Denervation of kidney Atropine Ergotamine	Reversed 0 Eliminated	0 Eliminated Eliminated

tion in uric acid excretion produced by the administration of ergotamine to gouty individuals and even the precipitation of an attack of gout. Hench,¹³ too, has mentioned two similar observations.

We have had a brief opportunity of studying one patient with pure gout under imperfect metabolic conditions. However, this patient is crucial in that careful investigation had revealed no other disease nor any involvement of the kidneys as such. The accompanying table shows the effect of a single injection of ergotamine on uric acid excretion in this patient. It seems significant that six or seven hours after the injection of the drug, reddening of and pain in the great toe occurred which the patient stated was precisely like his previous attacks which had occurred at sufficiently infrequent intervals to make the single observation of greater significance. The important result of the metabolic study is the diuresis produced by ergotamine with a smaller percentage increase in uric acid excretion. It is to be noted that in the four corresponding periods the creatinine excretion was in each period the same on the control day as on the experimental day, indicating in all

probability that the glomerular filtrate was of the same volume and that the differences produced by the injections of the drug concern reabsorption. Despite the absolute increase in uric acid excretion the concentration was diminished by ergotamine, indicating that the dose used was adequate to have an opposing effect to that of cinchophen. These facts might indicate that the gouty attack and uric acid excretion as such do not necessarily run hand in hand but none the less they are both connected with the autonomic mechanism which controls the concentration of uric acid in the urine. The effect of ergotamine on this gouty individual suggests that some impulses not normally present are acting on the uric acid excreting mechanism in this patient through the renal nerves, and that such impulses are capable of

TABLE II

Twelve hour excretion of J B S as affected by ergotamine. Identity of creatinine figures indicate similar volume of glomerular filtrate. Note the low concentration of uric acid accompanying the mild attack of gout. The blood uric acid remained unchanged, three samples in the first four hours ranging between 4.1 and 4.4 mg per 100 c c.

Period Number	Time	Control Day			Ergotamine 1 mg s c at 8 a m		
		April 9, 1937			April 7, 1937		
		Volume c c	Uric Acid mg	Creatinine mg	Volume c c	Uric Acid mg	Creatinine mg
1	7 a m - 1 p m	252	70	345	705	114	367
2	1-3 p m	220	45	160	300	37	130
3	3-5 p m	120	35	120	150	38	120
4	5-7 p m	220	40	144	175	40	159
Total		812	190	769	1330	229	776

modification by ergotamine in a similar fashion to its action on the stimulus provided by cinchophen.

If gout be a true functional disease of the autonomic nervous system, we should be able to discover in its symptomatology certain other features indicating such a disturbance. The diuresis of the gouty attack has been frequently observed. However, such patients have not been studied otherwise in relation to possible sympathetic disturbances. In the records of the Brigham Hospital, we have found 23 cases of gout without evidence of nephritis and these showed an average daily urinary volume of 1375 c c, as compared with 850 c c in random patients with nonmetabolic diseases in the hospital at the same time, indicating a continuing disturbance of the mechanism of water excretion. Since these cases were not studied at the time with this in mind, other clinical studies relating to the autonomic system are not available. Talbott, Jacobson and Oberg¹⁴ studied two patients and point out that a diuresis occurs before an attack of gout, however, their

tables show a continuing large urinary volume. It has been assumed that the diuresis of gout was an attempt to get rid of uric acid which the gouty kidney was unable to concentrate. However, it has been shown that the gouty kidney can concentrate uric acid as well as the normal¹⁵. Brugsch¹⁶ has emphasized the importance of the autonomic medullary centers in the control of purin metabolism.

The data collected here suggest that the etiology of gout may well be sought in functional disturbances of the vegetative nervous system involving especially the innervation of the kidney.

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LYMPHOSARCOMA CELL LEUKEMIA *

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It has been observed frequently that the blood of patients with lymphosarcoma may become leukemic. This syndrome has been characterized as leukosarcoma by Sternberg¹ or as lymphosarcoma terminating in lymphatic leukemia^{2, 3, 4}. Flashman and Leopold⁵ noted 107 cases of this type in the literature and described an additional case. On the basis of a lymphosarcoma presumably terminating in lymphatic leukemia, numerous speculations have been published concerning the relationship of these two conditions. A careful cytological study of the cell types in this form of leukemia has shown, however, that the cells are not lymphocytes, but lymphosarcoma cells, so that the condition is a true lymphosarcoma cell leukemia.

MATERIAL AND METHODS

Of 43 patients with known lymphosarcoma, 15 developed a leukocytosis during the course of the disease. This group comprised 10 males and five females. There were eight positive biopsies and six autopsies. The ages of the patients ranged from six to 70 years, with a fairly even distribution in the intervening decades, except that between 21 and 30 years, which included one third of the patients. Warthin⁶ noted leukemic transformation in nine cases of lymphosarcoma, out of a group of 134 biopsies.

To note how a lymphosarcoma cell would appear if it was in the blood stream, pieces of fresh lymphosarcoma glands were stirred in blood serum, and films were made of this suspension. These were stained with Wright's stain alone or preceded by brilliant cresyl blue while the cells were in the moist state.

THE LYMPHOSARCOMA CELL

The lymphosarcoma cell in the blood stream is usually mistaken for a lymphocyte. There are certain differentiating features, however, the most marked being the peculiar characteristics of the nucleolus. This is usually eccentrically placed, single, very rarely multiple. In the films made on brilliant cresyl blue containing cover glasses, later stained with Wright's stain, the nucleolus stands out as a sky blue, round area, surrounded by a deep, blue black rim of chromatin which is piled up around it. (Figure 1.) In the true immature lymphocyte or lymphoblast, under these conditions, the

* Presented to the Michigan Academy of Science, Arts and Letters, March 8, 1935, and, in abstract, to the American Society of Experimental Pathology, Washington, March 25, 1936 (Arch Path, 1936, *xxii*, 287.)

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nucleolus appears as a light blue "hole" or area in the chromatin structure, without the heavily staining rim. The nucleoli are more likely to be multiple in the immature lymphocytes or lymphoblasts than in the lymphosarcoma cell.

The lymphosarcoma cell, in films, varies in size from 7.5 by 9 microns to 12 by 13.5 microns. The nucleus is usually oval or oblong, occasionally being egg shaped (thicker at one end) in films. Kidney shaped or notched forms are common in some specimens. The stained chromatin is coarsely reticular and somewhat spongy in structure and the chromatin around the edge is thickened into a fairly definite nuclear wall, differing in this respect from the monocyte. The cytoplasm of the cell is sparse, deeply basophilic, and with the brilliant cresyl blue, Wright's stain, appears as a fine, blue lace-work.

In sections of fixed tissue, the lymphosarcoma cell is large and round, resembling the lymphoblast in size and proportion of practically non-granu-

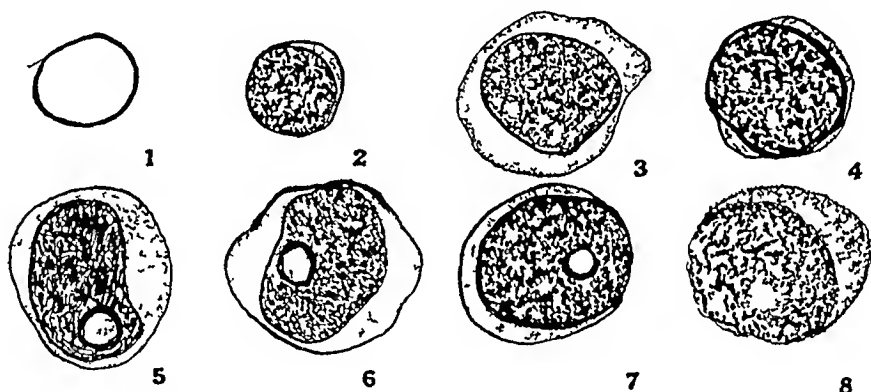


FIG 1 Cells from peripheral circulation. Stained supravitaly with brilliant cresyl blue and counterstained with Wright's stain. (Camera lucida drawings) 1-4 normal blood. 1 Normal red blood cell, for size comparison. 2 Small lymphocyte. 3 Large lymphocyte. 4 Large immature lymphocyte, with several small nucleoli. 5, 6, 7 Cells from lymphosarcoma cell leukemia. 8 Lymphocyte from lymphatic leukemia.

lar cytoplasm. The nucleus may be irregular in size and shape, many showing indentations or lobulation.

These cells were studied supravitaly by Wiseman⁷ who found that unlike mature lymphocytes, they did not show motility, although both types did not show evidence of phagocytosis. The mitochondria were described as dust-like, as compared to the large rods and spheres of the mature lymphocyte and the small spheres of the lymphatic leukemia cell. Deep scarlet neutral-red vacuoles, 1 to 10, were present at the periphery of the nucleus in the "sarcoma cell" although they were absent in the leukemic cell and, when present in the mature lymphocyte, they stained rose red.

THE BLOOD

There appear to be two phases of the blood in patients with lymphosarcoma—an aleukemic and a leukemic phase. In the aleukemic phase, the

leukocyte count varies from 6,000 to 10,000 per cubic millimeter with 30 to 40 per cent "lymphocytes" Many of these cells are not lymphocytes, but lymphosarcoma cells The percentage varies from 3 or 4 to 25 or 30 in this group In the leukemic phase, the count rapidly increases to an average of $70,000 \pm 43,200$ per cubic millimeter, the highest count in this series being 156,000 per cubic millimeter As the count increases, the bulk of the cells are lymphosarcoma cells, which in some cases form 98 per cent of the total

As the leukemic process progresses, anemia becomes more marked, the average red blood cell count being around 2.5 million per cu mm In some patients it reached a much lower level (0.8 to 1.0 million) The color index was most frequently around 1 or slightly below The blood platelets were increased in number in the early stages, but decreased in the late stages

CLINICAL COURSE

In most of the patients, enlargement of lymph nodes was the first sign noted Visible tumors in the neck region were the first evidence in three patients, inguinal nodes in two, mediastinal (cough, dyspnea, pleural effusion) in three, abdominal symptoms in two, sore throat in four, weakness in two and submaxillary enlargement in one Symptoms, in order of their frequency, were weight loss (average 15 pounds), fever, bleeding (petechiae, hemoptysis, hematuria, epistaxis, hematemesis, gross bleeding from mucous membranes, retinal hemorrhages), joint pains, pulmonary and hilar lesions (roentgen-ray changes, pleural effusion, dyspnea, chest pain, cough), allergic symptoms, herpes, skin lesions (toxic erythema, erythema multiforme), bone lesions, facial palsy, diplopia, local edema Albuminuria (trace), during some stage of the disease was common The spleen size varied from 15 to 23 centimeters (average 16.5 cm), and at autopsy the weights varied from 490 to 700 grams The spleen was palpable in seven patients

With the onset of the leukemic phase, fever was common (100 to 105° F) Terminally, 104° to 107° F were noted Lung involvement was not always definitely indicated on the roentgen-ray plates, although autopsy in some of these patients showed infiltration of the alveolar walls and of the perivascular and peribronchial tissue with lymphosarcoma cells This type of lesion was most common in patients dying in the leukemic state, whereas in two who were aleukemic on the day of death, the lungs were not involved The degree of leukemia was more parallel to the lung involvement than to the degree of peripheral lymph node enlargement

The duration of the disease varied from 2.5 to 36 \pm months The duration of the leukemic phase varied from two days to 60 days in eleven patients in whom approximate data were available One patient, however, gave a history of a leukemic blood picture (94,000 per cu mm), diagnosed as lymphatic leukemia, for over seven years This patient had a white

blood cell count of 37,000 when first observed at this clinic, with 84 per cent lymphosarcoma cells. He died 27 days later. The maximum count was 73,000. The average duration of the leukemic phase in all of the other patients was 26 days.

Nine patients gave a history of one or more of the common childhood diseases. Of the others, three gave a history of a symptom complex which they were told was influenza.

LYMPHOSARCOMA AND PREGNANCY

One patient with lymphosarcoma showed a remission during a period of pregnancy. The patient, a 31-year-old woman, was first studied after she had had cervical and axillary glandular enlargement for 18 months. Her blood count at that time was as follows: Red blood cell count 3,500,000 per cu mm, white blood cell count 47,800, hemoglobin 67 per cent (Sahli), 9.38 grams per cent, atypical "lymphocytes" 65 per cent, blasts 0.5 per cent. She became pregnant six months later, and during the third month she returned to the clinic for examination. At that time her red blood cell count was 4 million per cu mm, white blood cells 7,100 per cu mm, hemoglobin 12.93 grams per cent, polymorphonuclear neutrophils 71 per cent, large lymphocytes 15 per cent, small lymphocytes 9 per cent, monocytes 5 per cent. The adenopathy had practically disappeared. A perfectly normal child was born in due course of time, and eight months after this the blood count was still normal, but lymphosarcoma cells were noted on the blood films. About nine months after this, the patient returned in complete relapse, with a red blood cell count of 800,000 per cu mm, white blood cells 4,200, hemoglobin 2.88 grams per cent. Lymphosarcoma cells, 27 per cent, and one blast were noted. She received two blood transfusions and had another remission. An examination four months later showed her red blood cells at a level of 3,600,000 per cu mm, white blood cells 6,100 and hemoglobin 75 per cent (Sahli) (10.5 grams per cent), "lymphocytes" 59 per cent.

EFFECT OF ROENTGEN-RAY IRRADIATION

In 11 of the patients the leukemic phase started after roentgen-ray therapy, in two no roentgen therapy was given, and in two it is uncertain whether the patients had received roentgen therapy before they reported to the hospital or not. A decrease in the number of leukocytes followed roentgen-ray therapy during the leukemic phase, in 8 patients, with severe leukopenia (3,500, 1,800 and 350 per cu mm) developing in three patients. In five patients there was a subsequent increase in number after the initial decrease. There appeared to be two stages in the effect of roentgen-ray therapy, an initial decrease in the number of leukocytes, followed by a marked and rapid increase. Thus in one man with a leukocyte count of 50,000 per cu mm (96 per cent lymphosarcoma cells), 2800 r were given over 12 positions from May 20 to June 4. On the last day the count was

33,000 per cu mm Two days later the count was 156,000 per cu mm and the patient died In another patient the initial count was 10,500 leukocytes per cu mm On five successive days, 150 r were given The leukocyte count fell to 5,500 per cu mm It then rose gradually to 15,200 with 66 per cent lymphosarcoma cells 43 days later Three days before death, which followed in two weeks, the count was 92,000, with 85 per cent lymphosarcoma cells A third example is that of a patient with 7,800 leukocytes per cu mm, who received 1,200 r over a five day period At the close of the treatments the leukocyte count was 6,800 per cu mm An observation 41 days later showed that the count had increased to 50,000 per cu mm and three days later to 70,800 per cu mm The patient died within four weeks

PATHOLOGICAL CHANGES IN THE ORGANS

Autopsy studies of the organs of patients dying during the leukemic phase showed transformation, in varying degrees, of all lymphoid tissue in the body, into the lymphosarcoma type The lymphoid follicles of the intestine and colon, as well as the tonsil showed this change There was marked invasion of the bone marrow and subperiosteal extension, which also involved the surrounding tissues All of the organs showed invasion with lymphosarcoma cells Among those showing perivascular or tissue infiltration were the brain, capsule of the pituitary, the fatty envelope of all the organs (heart, kidneys, aorta), the myocardium, beneath the epicardium, bronchi, pulmonary alveolar walls, thyroid, esophagus, thymus, spleen, diaphragm, stomach, liver, gall-bladder, adrenal, kidney, ureter, skin, testes, epididymis, seminal vesicles and vas deferens The skull, when involved, showed osteolytic lymphosarcomatous infiltration

DISCUSSION

The frequent occurrence of the leukemic state of lymphosarcoma after roentgen-ray therapy is of interest in connection with the observations of Krebs, Rask-Nielsen and Wagner⁸ on the production of a "leukosarcomatosis" (aleukemic and leukemic) in white mice after irradiation They found that the leukemic phase developed late in the course of the disease, and that, as in the cases cited here, the prognosis was bad

In view of the tendency of the lymphosarcoma cell to invade the tissues, it is not surprising that some of the cells enter the blood stream However, it appears that the number does not reach leukemic proportions until there is extensive growth in moving organs, as the lungs This phenomenon is similar to that found in other types of leukemia (Isaacs⁹)

SUMMARY AND CONCLUSIONS

1 The characteristics of 15 cases of lymphosarcoma cell leukemia are given

2 The lymphosarcoma cell has characteristic cytologic features which facilitate its recognition in the blood stream. This cell type may constitute 4 to 98 per cent of the leukocytes in the peripheral circulation.

3 The leukemic phase is usually ushered in with exacerbation of symptoms and fever.

4 The leukocyte count may reach a maximum of from 23,000 to 156,000, and there is progressive anemia and thrombocytopenia.

5 The duration of the leukemic phase varies from two to 60 days (average 26 days) although one patient had a history of leukemia for over seven years.

6 There may be relapses and remissions, but the prognosis is poor. A temporary remission may be induced by roentgen-ray therapy, but this is followed by a relapse and death.

7 The disease appears to be a true lymphosarcoma cell leukemia, rather than lymphosarcoma turning into lymphatic leukemia.

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THE FLOW AND CONCENTRATION OF BLOOD AS INFLUENCED BY ERGOT ALKALOIDS AND AS INFLUENCING MIGRAINE *

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IN about 90 per cent of patients suffering from an attack of migraine headache, the injection of ergotamine tartrate causes complete disappearance of the pain and other symptoms ¹ In the case of the more recently isolated alkaloid of ergot, ergonovine, clinical results are not so striking In our 54 patients who received injection of the drug, pain was stopped in 39 per cent and was improved in a further 40 per cent ² The beneficial action of ergot seems to be specific for headaches of the migraine type ³ These welcome therapeutic results led us to investigate the physiological effects of these ergot derivatives

In this communication we report the action of ergotamine and of ergonovine on the speed of flow and on the concentration of blood as revealed by measurement of blood gases No observations of blood flow have been reported for ergonovine As for ergotamine tartrate, Lennox, Gibbs and Gibbs,⁴ by means of a thermoelectric flow recorder inserted in an internal jugular vein of migraine patients, obtained records showing an increase of cerebral blood flow after intravenous injection, presumably a result of the coincident increase in blood pressure On the other hand, Herrick,⁵ in dogs, obtained large increases in blood pressure but a decrease in blood flow which, on the average, was only one-fourth its initial value Presumably, the difference in results can be accounted for by the fact that his dogs received a dose three or four times that used by us in human subjects

Because epinephrine has been considered pharmacologically as the antagonist of ergotamine, parallel observations were made with this drug

MATERIALS AND METHODS

Epileptic and other patients on the Neurological Service at the Boston City Hospital were used for these observations Subjects were in bed but not fasting Blood was drawn from the arm without stasis under oil, chilled and analyzed at once in the apparatus and by the technic of Van Slyke ⁶ After the preliminary blood sample was taken, the subject was given either ergotamine tartrate, 0.5 mg intravenously, or ergonovine, 0.6

* Received for publication July 29, 1937

From the Neurological Unit of the Boston City Hospital and the Department of Neurology of Harvard Medical School, Boston, Mass The research was aided by the Josiah Macy, Jr Foundation

mg intravenously or 12 cc by mouth, or epinephrine, 0.1 mg subcutaneously^{*} Records were kept of the subject's blood pressure and pulse rate and of his symptoms The second blood sample was taken after a lapse of from 30 to 60 minutes (the interval required for ergotamine to stop a headache) After epinephrine injection, the interval was 40 to 70 minutes, the effort being to secure blood while the reaction was at its height

Ordinarily, an alteration in blood flow would be shown by an alteration of oxygen content, but when the concentration of red cells is changing, measurement of the oxygen saturation also is necessary The percentage of saturation was obtained by dividing the oxygen content of the blood by its oxygen capacity Changes in the oxygen capacity of the blood represent changes in the concentration of the red cells Results will first be stated, then discussed

EFFECT ON OXYGEN SATURATION OF VENOUS BLOOD

Ergotamine Tartrate Fourteen observations were made of changes in the blood gases of the venous blood of the arm following the intravenous injection of ergotamine In all these observations there was a wide scattering of individual results, but nearly all were in the same direction After injection of ergotamine, in three instances there was a decrease of oxygen saturation and in 11 an increase The average change was an increase of 8.1 per cent (i.e., from an oxygen saturation before injection of 63.5 per cent to 71.6 per cent saturation after injection) (See the accompanying table) The percentage increase in the average oxygen saturation of the blood (12.7 per cent) was not as great as the percentage increase in its oxygen content (17.7 per cent), because the oxygen capacity of the blood also increased

Ergonovine Eighteen patients were given ergonovine (*Ergoklonin*) In six instances, administration was intravenous, and in 12 instances, by mouth The average oxygen saturation of venous blood showed a definite increase of 10.6 per cent when the drug was injected and of 4.2 per cent when it was ingested A change greater after intravenous injection than after ingestion was to be expected The greater effect of ergonovine than of ergotamine is explainable by the larger dose contained in an ampule of ergonovine

Epinephrine This drug was injected in 13 instances Results were less uniform than in the case of ergot A decrease in the oxygen saturation

^{*} Ergotamine tartrate (*Gynergen*) was supplied by the Sandoz Chemical Works, Inc., of New York, and ergonovine (*Ergoklonin*), by John Wyeth and Brother, Inc., of New York Each of these firms also contributed funds for the research Ergonovine was so named by the Council on Pharmacy and Chemistry of the American Medical Association *Ergoklonin* is a trade name The preparations of *Ergoklonin* furnished us, being brownish in color, presumably contained ingredients other than ergonovine, which in solution is clear *Ergoklonin*, however, had an action similar to other preparations of ergonovine in the clinical and laboratory tests which we used, 0.2 to 0.3 mg of ergonovine is equivalent to about 0.5 mg of ergotamine

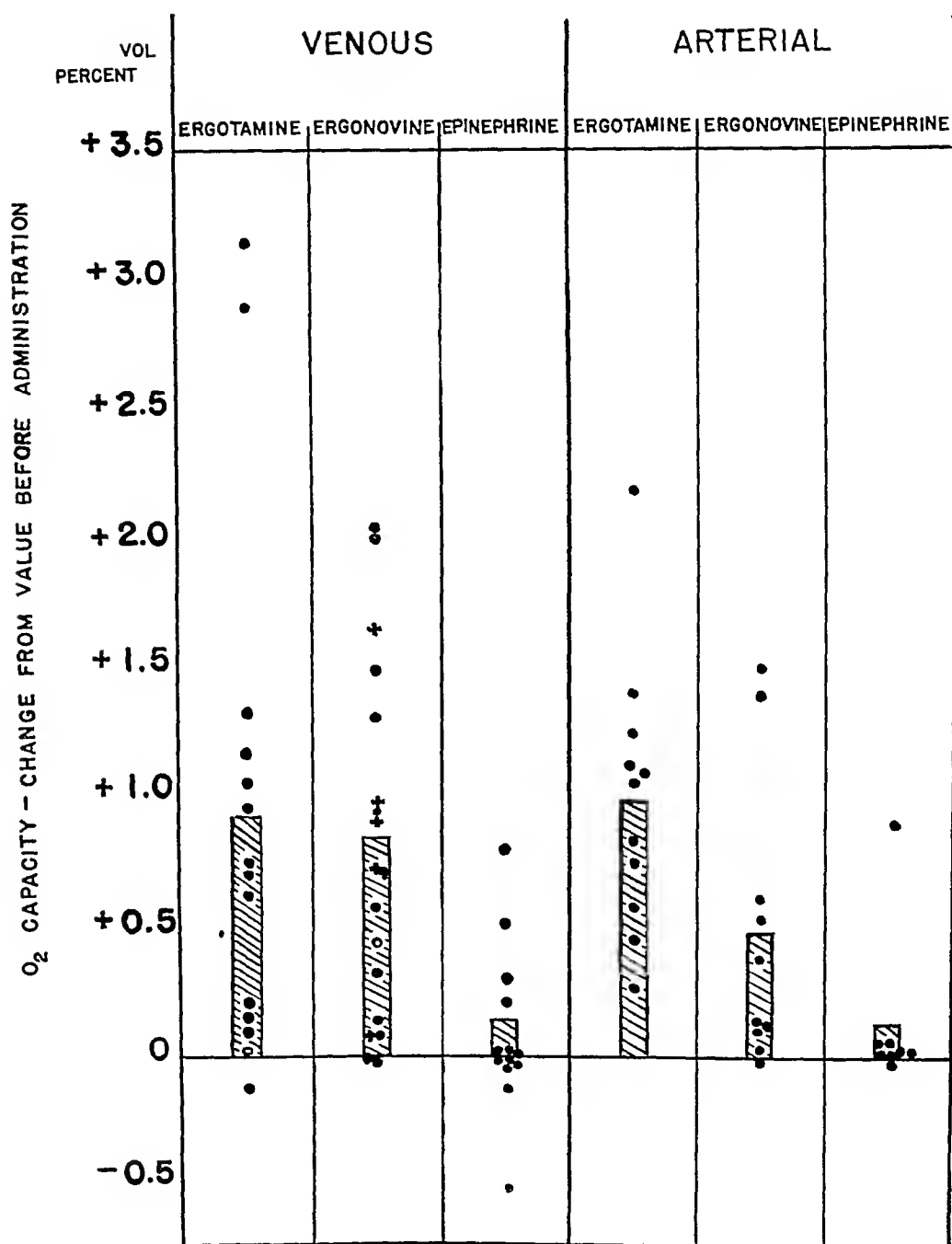


FIG 1 The average and individual measurements of the change in the oxygen capacity of venous and arterial blood following the administration of ergotamine tartrate, ergonovine (*Ergoklonin*), and epinephrine. The ordinate represents the absolute change in the oxygen capacity in volume per cent. The columns indicate the average measurements for the group, and the dots, the individual measurements. The ergotamine was given intravenously in all cases. The *Ergoklonin* was given by mouth except for those experiments in the venous column which were marked by crosses. Crosses in this compartment indicate medicine given intravenously. The epinephrine in all cases was given subcutaneously.

occurred in four of the 13 observations and the average change was an increase of 5.8 per cent

Discussion In resume, the increase in the average absolute per cent saturation of venous blood for the various groups, as well as the percentage increase over the preliminary measurements was as follows

			Absolute Increase Per cent	Percentage Increase
Ergotamine tartrate	I V	14 cases	8.1	12.7
Ergonovine	I V	6 cases	10.6	18.6
Ergonovine	P O	12 cases	4.2	8.0
Epinephrine	S C	13 cases	5.8	8.9

An increase in the oxygen saturation of venous blood means either a decrease in the consumption of oxygen on the part of the tissues through which the blood passes or an increase in the rapidity with which the blood flows through the part. Epinephrine increases oxygen consumption, whereas in normal persons, ergotamine does not.⁷ However, most subjects were more restless after injections than before, and their metabolic rates were presumably increased, therefore the increase in the speed of blood flow through the arms, especially in the case of epinephrine, was probably greater than the measurements indicate. An increased cerebral blood flow following injection of epinephrine⁸ and of ergotamine⁴ has been demonstrated by other methods. The increased cardiac output from epinephrine is well known.

Effect on Oxygen Saturation of Arterial Blood Thirty-one observations were made of arterial blood before and after the injection or ingestion of these three drugs. As would be anticipated, changes in the average oxygen saturation were negligible. Ergonovine given by mouth and epinephrine injections caused no significant alterations. After injection of ergotamine, the oxygen saturation decreased by 2.2 per cent. This decrease did not, of course, indicate a decrease of blood flow, the blood being arterial, but was due to an increase in the oxygen capacity of the blood. The oxygen content of the blood did not keep pace with the increase in its capacity, due possibly to an increased speed of blood flow through the capillaries of the lungs which allowed less time for the transfer of oxygen to the blood.

Effect on Oxygen Capacity of Venous Blood After injection of ergotamine, the oxygen capacity of venous blood was increased in all experiments save one. The average increase was 0.90 volumes per cent (from 19.46 volumes per cent before, to 20.40 volumes per cent after the injection). Increase of a comparable magnitude occurred after ergonovine (0.84 volumes per cent when given intravenously and 0.86 volumes per cent when given by mouth). The changes after injection of epinephrine were variable and the average increase was only 0.15 volumes per cent. Average results appear in the table and both average and individual results are indicated in the figure.

Effect on Oxygen Capacity of Arterial Blood The average increase in the oxygen capacity after ergotamine injection was 0.98 volumes per cent, and after epinephrine injection, 0.11 volumes per cent. After ergonovine taken by mouth, the average increase was 0.47 per cent which was less than the increase which occurred in venous blood. The average changes in arterial blood after ergotamine and epinephrine were almost identical with those occurring in venous blood.

Consolidating the observations for venous and for arterial bloods, the oxygen capacity of blood was increased by these drugs on the average as follows

			In Vol Per cent	Percentage Increase
Ergotamine	I V	27 cases	0.94	4.8
Ergonovine	I V	6 cases	0.84	4.4
Ergonovine	P O	22 cases	0.68	3.5
Epinephrine	S C	21 cases	0.13	0.6

Quantitative results therefore differ, the increase being of a different order for ergot derivatives than for epinephrine.

Edmunds and Nelson⁹ have reported that the subcutaneous injection of epinephrine in 10 dogs caused an average increase of 23 per cent in the number of red cells of capillary blood. The relatively small change which we observed is probably due to the fact that they injected 50 to 70 times the amount of epinephrine we used. They attribute the polycythemia both to a loss of blood plasma and to the addition of red cells swept from the bone marrow. We have no direct evidence as to which of these changes was responsible for the increased concentration of arterial and venous blood which follows the administration of ergot derivatives.

Inspection of the table shows that, irrespective of changes in the average oxygen content of the blood, the average carbon dioxide content decreased in each of the four different experimental procedures. We believe this decrease was due to increased pulmonary ventilation associated with the restlessness which followed the injection of the drugs.

Discussion We have observed then that the ergot derivatives, ergotamine tartrate and ergonovine, cause moderate increase in the speed with which blood flows through the arm as measured by the oxygen saturation of the venous blood. This increase presumably is due to the increase in blood pressure which occurred in these cases.² The increased pressure presumably followed a mild constriction of peripheral arteries. Pool and Nason¹⁰ observed constriction of dural and skin vessels in animals. In order to account for increased blood flow, the peripheral vasoconstriction, if generalized, must be more than counterbalanced by the cardiac output. The beneficial results of ergot cannot be attributed solely to the increased blood flow, because similar increase in flow took place when adrenalin was injected, but only in a minority of cases is the use of adrenalin followed by relief of migraine headache.

There was an increase in the concentration of the blood following the administration of ergot. The average degree of concentration differed for the three drugs used, the order being ergotamine, ergonovine and epinephrine. This is the same order in which these drugs are effective in stopping migraine attacks. In fact, the quantitative differences between the ergot fractions on the one hand and epinephrine on the other are so great as regards their effect on headache and on the concentration of blood that alterations of blood concentration might be suspected of playing a dominant rôle in migraine headache. We do not believe, however, that relief of migraine attacks is due simply to a concentration of red cells in the blood. If it were, therapeutic results in migraine would have been reported in conditions associated with dehydration of the blood, such as starvation, purgation and profuse sweating.

There is indication, rather, that ergot in the therapeutic doses employed, causes a "tightening up" of the blood vascular system, an increased tone to arteries whose tone may have been impaired, increase in blood flow and possibly of cardiac output, and a decreased volume along with an increased viscosity of the blood. These observations would seem to dovetail with those of Wolf,¹¹ who, after ergotamine injection, observed a 50 per cent reduction in the pulsation of temporal arteries of patients having migraine headache, the reduction paralleling in time the relief from headache. The increase of spinal fluid pressure which follows injection of ergot, reported by Pool, von Storch and Lennox,¹² might be due to a transfer of fluid from cerebral capillaries. Also, Pool and Nason¹⁰ observed consistent constriction of dural and skin vessels after ergotamine, whereas pial vessels behaved variably. The dural vessels are presumably more at fault in migraine headaches than those in the cerebrum. Our observations, therefore, may form a link in the explanation of the mechanism of migraine headaches when such explanation is complete. The final chain of reasoning must, however, be distinctive for migraine as contrasted with non-migraine headaches, and must explain not only the headache, but the visual, the sympathetic and the peripheral sensory disturbances which form a portion of the migraine syndrome.

SUMMARY

Ergotamine tartrate was administered to 27 subjects, ergonovine to 28 and epinephrine to 21, in order to observe the effect on the flow and the concentration of blood as measured by changes in the concentration of blood gases.

The parenteral administration of ergotamine, of ergonovine and of epinephrine produced a percentage increase in the average oxygen saturation of venous blood from the arm of 12.7 per cent, 18.6 per cent and 8.9 per cent respectively.

The ergot derivatives injected intravenously produced a definite increase in the oxygen capacity of both venous and arterial blood, the combined percentage increase being for ergotamine, 48 per cent, and for ergonovine, 44 per cent. In contrast, epinephrine caused insignificant increase, 0.6 per cent.

Therefore, these ergot derivatives, like epinephrine, cause increase in the rate of blood flow through the peripheral tissues. Unlike adrenalin, ergotamine and ergonovine concentrate the blood. The specific effect of ergotamine and of the less effective ergonovine in relieving migraine headache may be partially explained by their action in increasing the tone of arteries. Increase in blood pressure and blood flow and decrease in blood volume may be the result of the increase in arterial tone. These observations may form a link in the chain of reasoning which ultimately will explain the mechanism of migraine.

Effect of Ergotamine Tartrate, of Ergonovine, and of Epinephrine on Blood Gases

Arm Vein	No of Cases	O ₂ Content Vol %	O ₂ Capacity Vol %	O ₂ % Satura- tion	CO ₂ Content Vol %
Ergotamine, I V Before After	14	12.38 14.58	19.46 20.40	63.5 71.6	53.36 51.46
Ergonovine, I V Before After	6	10.76 13.50	19.09 19.93	57.0 67.6	56.23 51.48
Ergonovine, P O Before After	12	9.72 11.26	18.91 19.77	52.1 56.3	56.03 54.54
Epinephrine, S C Before After	13	13.06 14.28	20.26 20.41	64.5 70.3	52.71 47.12
Arterial					
Ergotamine, I V Before After	13	18.61 19.18	19.54 20.52	95.7 93.5	47.97 46.88
Ergonovine, P O Before After	10	19.00 19.49	20.30 20.77	93.5 93.9	46.55 46.37
Epinephrine, S C Before After	8	19.09 18.96	20.24 20.35	94.1 93.2	48.15 47.77

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INTRAVENOUS LIVER EXTRACT IN THE THERAPY OF PERNICIOUS ANEMIA, REPORT OF A CASE *

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It is a common observation that patients with pernicious anemia may fail to respond to the oral administration of liver, liver extract and ventriculin, and that these same patients will respond promptly to an extract given intramuscularly. Satisfactory and more rapid improvement in the patient's blood has been frequently noted after intravenous injection of specially prepared liver extract^{1, 2, 3, 4, 5}. However, this intravenous therapy is not in general use because of the side reactions noted in many cases.

The case of pernicious anemia reported in this paper is of interest because on the first admission the patient responded in a characteristic manner to the administration of liver extract intramuscularly and subsequently he had a relapse. On further treatment a progressive aplastic state continued despite the administration of oral liver, intramuscular extract, ventriculin and blood transfusions. Finally liver extract given intravenously resulted in a prompt and complete remission.

CASE REPORT

E L J, white farmer, aged 62, admitted to the hospital on November 19, 1934, complaining of weakness and generalized aching of three weeks' duration. Five years before his admission, while working for the State Highway Department he noted an increasing weakness which progressed finally to the point of difficulty in walking. There was no numbness or tingling. He was admitted to a Washington hospital where a diagnosis of pernicious anemia was made and he began taking liver by mouth. After a year's rest he was again employed and continued work for eight months. At the end of this period he reported that while cranking a car he felt something "give way inside of him," and that he had been unable to work since then. The patient's therapeutic regime was now changed to liver extract per os and later it was given intramuscularly. His treatment had been most irregular and he described periods of weakness coinciding with the times in which he had no therapy. Three years ago a lumbar puncture was done and he stated that he has been unable to walk since that procedure. Four blood transfusions had been administered during the past year. Three weeks before admission his local physician advised hospitalization because of weakness, palpitation of the heart and poor appetite.

The physical examination revealed an undernourished, elderly, pale man. The mucous membranes were pale and the sclera lemon tinged. The tongue was smooth and glistening. The heart, lungs and abdomen were normal. The blood pressure was 110 mm of Hg systolic and 45 diastolic, pulse 112, and there was slight pitting edema of the shins. A bilateral hydrocele was present. The patellar reflexes were hyperactive, ankle clonus was present and there was a positive Babinski sign. The vibratory sense was absent below the knees. The patient could not walk.

* Received for publication August 4, 1937

From the Department of Internal Medicine, University of Virginia Hospital

Laboratory examinations showed the following Hemoglobin 22 per cent (Dare), red blood cells 1,900,000, white blood cells 3,000, with band cells 4 per cent, segmented 51 per cent, small lymphocytes 43 per cent, large mononuclears 2 per cent. The platelet count was 137,000, the reticulocytes 15 per cent, color index 52, volume index 42, and the icterus index 15. The smear showed the red cells to have a marked anisocytosis with many microcytes, a few macrocytes, moderate poikilocytosis, and a moderate diffuse polychromatophilia was present. One normoblast was seen. No free hydrochloric acid was present in the stomach contents after the injection of histamine. The Wassermann and Kahn were negative.

From the history and findings a diagnosis of pernicious anemia was made and intramuscular liver therapy inaugurated. After one week of treatment the volume index changed to 12 and the color index to 12. The patient responded typically to this therapy as indicated in chart 1. Throughout his stay in the hospital he was

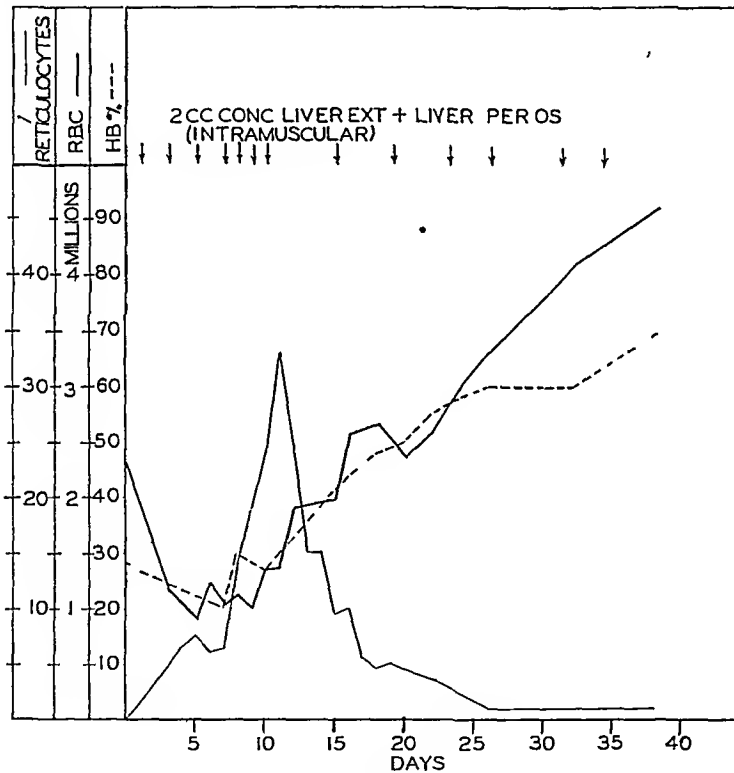


CHART 1

given iron and ammonium citrate, 90 grs daily. On discharge 41 days after admission he had improved in all respects, and he could move his legs without difficulty.

After leaving the hospital this patient took his liver extract intramuscularly (2 cc) once weekly for a while, then the interval between treatments became lengthened to every two weeks and finally once a month. He again became progressively weaker, with all of his old symptoms returning. On December 29, 1935, the patient was readmitted. In the period between the two admissions he had not been able to walk. The physical examination showed that the patient was again pale and thin. The blood pressure was 96 mm of Hg systolic and 54 diastolic, and the knee jerks hyperactive, ankle clonus present with bilateral positive Babinski. On the whole he was in the same physical state as on the previous admission. Laboratory

examinations showed a hemoglobin of 35 per cent (Dare), red blood cells 1,740,000, white blood cells 2,800, and the differential essentially the same as on the last admission. The smear showed many macrocytes and a few poikilocytes. The color index was 1.3, volume index 1.4, reticulocytes 0.2 per cent, and the icterus index 10.5. A mild cystitis was also found to be present. A gastrointestinal roentgen-ray series was negative.

The patient was given 10 cc of concentrated intramuscular liver extract (Eli Lilly) followed by 2 cc of the same preparation every four days. In spite of this therapy there was very little reticulocyte response, the red count and hemoglobin decreased and the patient showed a progressive loss of strength and appetite. Parke Davis' intramuscular extract was then given and blood transfusions, liver by mouth and ventriculin were all tried with only temporary effect. Finally it was decided to give an intravenous preparation*. Twenty cubic centimeters were administered intravenously very slowly and this was followed by a chill and a temperature of 104° F. Following this the patient showed improvement in his condition, the reticulocytes rose and the blood picture in general showed evidence of the influence of the active principle in liver. On each subsequent injection of liver intravenously (five in all) the reactions became decreasingly severe with only slight flushing of the face and a little shortness of breath. Iron and ammonium citrate (90 grains daily) was given from the day of admission to the day of discharge. The essential data are given in chart 2. The patient was discharged 120 days after

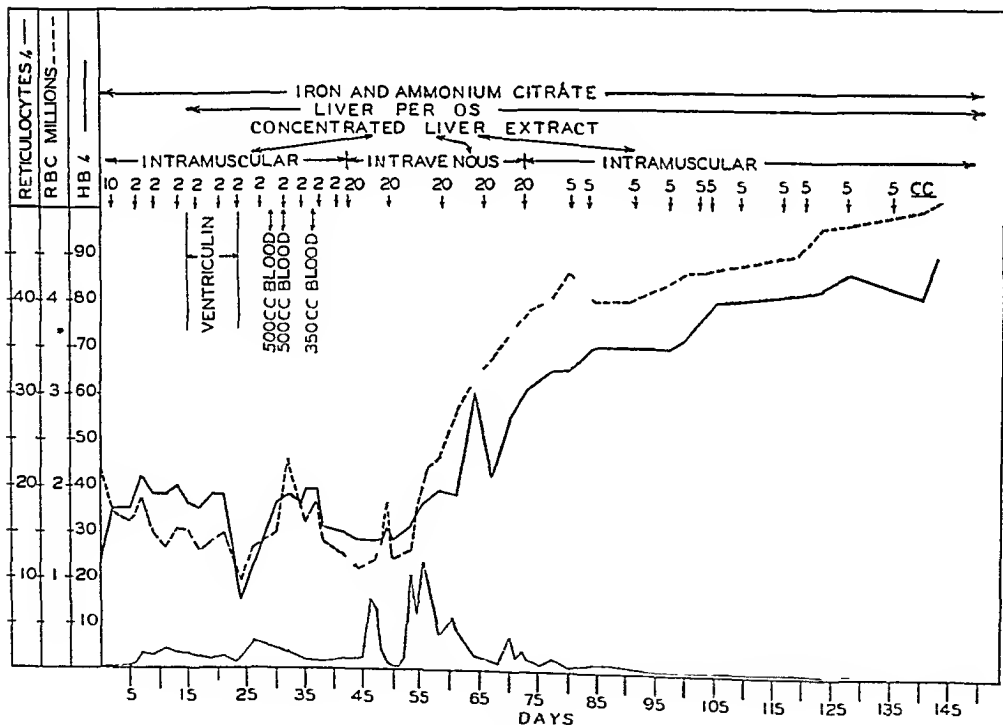


CHART 2

admission in good general condition, with a normal blood count, but he was still unable to walk. He is being maintained at home in a good state of health with a normal blood picture by an intramuscular injection of 2 cc of liver extract once a week.

* An intravenous extract prepared by Parke Davis Co was obtained through the courtesy of Dr Raphael Isaacs, Ann Arbor, Mich.

COMMENT

In a review of the literature no mention was found of a similar case of pernicious anemia. Rhoads and Miller⁶ cite two cases of sprue that failed to respond to intramuscular extract but recovered promptly when the extract was given intravenously. Castle et al.⁷ also emphasize the importance of intensive parenteral therapy in this condition. One can only speculate with respect to the failure of this patient to respond to the usual therapeutic procedures used in treating pernicious anemia. The only evidence of infection was found in the bladder and it seems doubtful that this was sufficient to prevent an adequate response.

Minot⁸ has called attention to the importance of adequate quantitative treatment in pernicious anemia, and it is possible that in this case the amount of liver used was not sufficient even when given intramuscularly. The only alternative explanation that can be offered is that the extract was not utilized which seems doubtful in view of the subsequent control by the intramuscular preparation. It is thought, however, that the case presents a method of dealing with an interesting therapeutic problem which might be useful in similar situations.

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FAMILIAL SHIFT TO THE LEFT OF THE LEUKOCYTES (PELGER'S NUCLEAR ANOMALY OF THE LEUKOCYTES), WITH REPORT OF A CASE^{*}

By WILDER TILESTON, M D , *New Haven, Connecticut*

IN 1928 Pelger⁶ reported to the Dutch Pathological Society at Amsterdam two cases showing an anomaly of the leukocytes, hitherto undescribed in the literature. The neutrophils, eosinophils and basophils all showed a large percentage with non-segmented nuclei, and the segmented forms were represented almost exclusively by those with only two nuclei. Furthermore, the nuclei differed from those met with in the ordinary shift to the left of infectious diseases, in that they had a remarkably regular shape with even contours. The protoplasm of the neutrophils on the other hand showed fine even granulations, of the type seen in mature cells. His first case was a woman who suffered from cachexia of obscure origin, and died of a terminal pulmonary infection, there was no autopsy. His second patient was a man with splenomegaly, material obtained by puncture of the spleen was injected into a guinea-pig and caused tuberculosis in the animal. Pelger believed that the anomaly of the leukocytes was pathological, in some manner connected with tuberculosis, and of bad prognostic import.

Three years later Huet⁴ discovered a similar hemogram in a niece of Pelger's first patient, and investigating other members of the family, found it in them also. He was therefore the first to recognize the familial character of the anomaly, and since it was present in healthy people, he declared it to be without pathological significance. Huet also reported two other families with this condition, there was no interrelationship between these families.

Other reports soon followed, so that up to the present time there have been recorded five such families in Holland, three in Germany, one each in Switzerland, Czechoslovakia, and the United States. It has been shown that the anomaly is inherited as a dominant Mendelian character, not sex-linked.

The following case, taken from the writer's private practice, seems worthy of record. It is the second to be reported in this country, and the first involving a person of English ancestry, Peterson's⁷ publication having concerned a Chinese family.

CASE REPORT

The patient, a lawyer now 73 years of age, has been under the writer's care for the past 26 years. In January 1918 he had an attack of lobar pneumonia of moderate

^{*} Presented at the Annual Meeting of the Association of American Physicians, May 5, 1937

severity, with high fever and terminating by crisis, the leukocyte count was 16,600 with 82 per cent neutrophils. In November 1918 he had influenza, with a temperature of 103 degrees and a leukocyte count of 3,500, no differential count was made. These facts are interesting as indicating a normal reaction to infection on the part of the bone marrow.

For the remainder of this long period he has had no serious illnesses, and is now in good health and active in the practice of his profession.

Five years ago he had an attack of syncope, the cause of which was undetermined, and a routine examination of the blood disclosed the fact that, although there were no signs of infection and the total leukocyte count was normal, more than half of the neutrophils were non-segmented or staff forms, and that the nuclei of the remainder had, almost without exception, only two lobes. This curious condition has persisted ever since, with little change in the relative proportions (table 1). Most

TABLE I

Date	Red Cells Millions	Hgb %	Leuko-cyte Count	Neutrophiles		Lymphocytes	Mono-cytes	Eosino-philes	Baso-philes
				Staff Cells	Segmented Cells				
11-18-31	4.4	70	8,600	34	26	22	9	9	0
12-18-31	4.9	75	7,100	26	16	39	11	8	0
1-6-32	—	—	—	34	24	17	15	10	0
3-15-32	—	75	6,200	46	16	30	5	3	0
6-13-32	—	75	6,000	43	19	29	4	5	0
12-5-32	—	70	7,700	47	17	23	4	9	0
5-13-33	—	75	5,300	32	24	36	6	2	0
10-13-33	—	80	5,000	36	15	33	12	3	1
7-31-34	—	80	5,800	32	21	30	10	4	3
4-18-35	—	80	—	36	30	25	4	5	0
11-11-35	—	80	—	36	25	29	8.5	1.5	0
11-11-36	—	80	—	32	22	30	10	5	1
4-28-37	3.4	75	6,100	38	24	27	8	3	0
6-2-37	4.7	88	7,800	43	21	27	5	3	1

of the smears have shown no nuclei with more than two lobes, rarely one with three lobes has been present (up to 1.5 per cent in the differential count), but never any with more than three lobes.

The appearance of the nuclei of the neutrophils is unusual, the contours being smooth and regular, in contrast with the irregular shapes seen in the ordinary shift to the left, and in normal blood. A fair number of the non-segmented forms (up to 12 per cent of all neutrophils) might be classified as "juvenile," by reason of their broad kidney-shaped nuclei, no myelocytes were encountered. The segmented cells have two oval or round nuclei, connected by a fine thread.

The protoplasm of the neutrophils shows no abnormalities, toxic granulation and vacuolization being uniformly absent.

The eosinophils are affected in a similar way, but to a less marked degree, a differential count of 100 eosinophils showing 38 per cent non-segmented, 62 per cent two-lobed, none with more than two lobes. It should be noted that in normal blood segmentation of the eosinophils is not carried out to the same extent as it is in the case of the neutrophils, 76 per cent having two nuclei, and only 19 per cent more than two. However, staff cells normally make up only 3 per cent of the total, according to Zundel.¹⁰

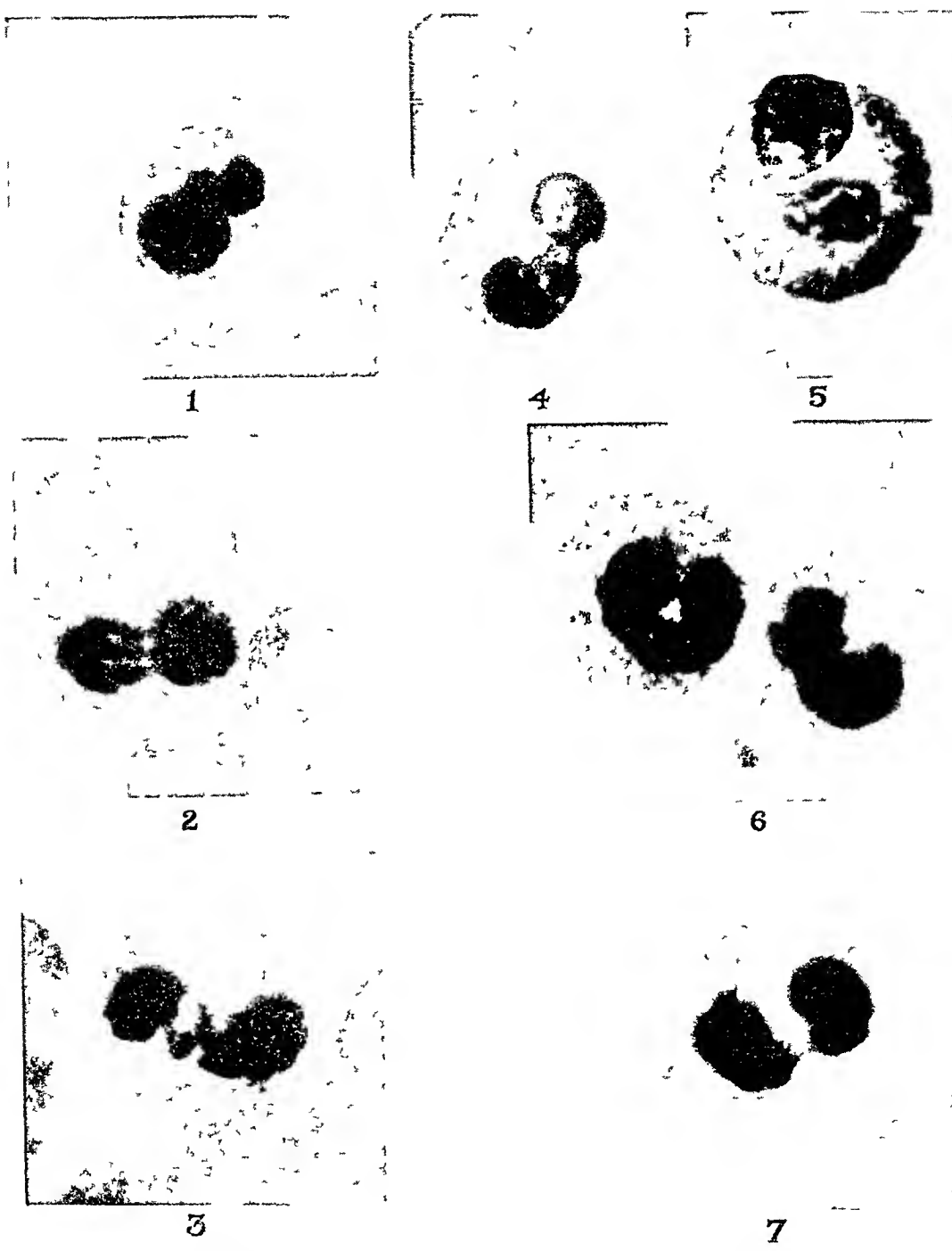


FIG 1 Photomicrographs of polymorphonuclear leukocytes No 5 shows an eosinophile, others are neutrophils Leishman stain, magnification approximately 800

It was difficult to determine whether the basophiles were involved or not, on account of the scarcity of these cells, and their frequent failure in normal blood to show clear-cut segmentation into several nuclei

When treated with Goodpasture's stain, all of the neutrophils showed abundant oxidase granules. In a supravital preparation examined by Dr R M Thomas, all of the granulocytes showed motility, and no abnormal granulations were present

An attempt to estimate the phagocytic activity of the leukocytes, made by Prof George H Smith, disclosed an interesting phenomenon, hitherto undescribed in this condition, on centrifugation of the ovalated blood, the leukocytes gathered together into a sticky mass, so cohesive that it was impossible to draw them up into a pipette, or smear them on a slide. No explanation of this curious behavior was forthcoming

The differential count was normal, so far as lymphocytes, monocytes and basophiles were concerned. A tendency to eosinophilia (up to 10 per cent) was present, for which no cause was apparent, it is interesting to note that a grandnephew of the patient, otherwise healthy and not showing the anomaly, had 18 per cent eosinophiles. In some of the cases reported in the literature eosinophilia has been present but not often enough to suggest any connection with the anomaly

The red count, hemoglobin, and total leukocyte count were within normal limits, apart from a trifling anemia, and the red cells showed no abnormalities. The platelet count was 240,000, the reticulocytes numbered 0.8 per cent. The coagulation time was 8 minutes, the bleeding time $1\frac{1}{2}$ minutes. The patient's blood group is "A" (international nomenclature). The sedimentation rate was not determined

Investigation of the relatives of the patient was disappointing. He has had no children, and both his brothers are dead. Examination of smears of all the children and grandchildren of these brothers, to the number of eight, and of two cousins, failed to reveal the anomaly in any of them. It is therefore impossible to state positively whether the condition in this person is familial or not, but since all of the cases reported in the literature have been familial, it may be assumed that it is

The family history reveals a tendency to arterial disease. One brother died at 50 of a ruptured aneurysm of the iliac artery, the result of atheroma, the other died suddenly, of coronary occlusion, at the age of 57. The only sister was still-born. The father, however, lived to the age of 96

Physical examination, April 22, 1937. Age 73 years. A tall thin man weighing 148 pounds. Color fair, pupils equal and react to light, arcus senilis present, sclerae faintly yellowish. Mouth and throat negative. Thyroid gland and lymph nodes not enlarged. Heart of normal size, action regular, there is a rather loud systolic murmur in the aortic area, transmitted towards the neck. Pulse rate 56, blood pressure 104 systolic and 58 diastolic, the peripheral arteries are moderately thickened. Abdomen natural, liver and spleen not enlarged. Knee jerks and plantar reflexes normal. On the skin of the neck and upper part of the chest anteriorly there are numerous rounded or flattened papules of a yellowish-white color, a biopsy was done, and a diagnosis of multiple benign cystic epithelioma was made. The urine is negative. Wassermann and Kahn tests of the blood negative. Blood group "A" (international nomenclature). The patient has shown a pronounced arcus senilis and a systolic murmur in the aortic area since the age of 47 years

DISCUSSION OF THE LITERATURE

The blood picture as first discovered by Pelger has been verified by all subsequent observers. Unfortunately Pelger's description is not to be found in print, except as quoted by some of the Dutch writers, for the account of his original communication to the Dutch Pathological Society⁶ merely alludes to a demonstration of two patients with a rare anomaly of the

leukocytes, without any description of the blood picture, the promised extensive article on the subject never appeared. Staff cells have been present in large numbers in all cases, and have almost invariably exceeded the segmented forms. Cells with more than two nuclei have been found rarely, or not at all. The shift to the left has gone as far as juvenile cells, but myelocytes very seldom have been noted, and then in small numbers (0.5 per cent, Schilling). The proportion of juvenile cells has varied widely, as might be expected on taking into account the element of subjectivity in the classification of this form of cell. Schilling, on examining smears from 11 cases, found the juveniles making up the majority of the non-segmented cells, but Undritz recorded only from 2 to 9 per cent.

All authors are agreed that the eosinophiles are involved in the shift, but as regards the basophiles opinions are divided. No extensive studies of the basophiles have been made.

Toxic granulation of the protoplasm of the neutrophils has been absent, except in one of Zundel's cases.

The response to infection has been reported only in one instance, in one of Huet's cases during an acute unspecified infection the percentage of staff cells rose from 26 to 44 per cent.

No studies of the bone marrow have been made, nor have any autopsies been performed.

The sedimentation rate has been normal in all the cases in which it has been measured, in contrast to the increased rate met with in the infectious shift to the left.

Blood grouping seldom has been determined, Jordan's patient belonged to group "O," the writer's to group "A."

The familial character of the anomaly has been proved in all the cases reported up to the present time, with the exception of Pelger's second patient, and the case of Chevallier and Ély,³ in both of which the relatives were not investigated. The trait has been found present in three generations by Huet, Jordans⁺ and Peterson. It has been transmitted by both sexes, and males and females are affected in equal proportions (exactly 50 per cent of each). It is therefore not sex-linked. In no case have the offspring of unaffected members shown the anomaly. The proportion of the affected among the children of affected parents has varied from 50 to 100 per cent, Aheff and Reekers found 7 out of 14 affected, Huet 3 out of 6, Jordans 6 of 9 in the second generation, 3 of 6 in the third, Zundel 4 of 6, and 3 of 4 in the second and third generations respectively. The highest incidence was in the family of Undritz, in which all of 5 living members of the second generation were affected (two had died without investigation), and all of 3 siblings in the third generation. In no instance have both husband and wife been proved to be bearers of the trait.

* Jordans' family is identical with family "Q" of Burger, the family tree is completed in Burger's article.

It is thus apparent that the anomaly is a dominant Mendelian character, not sex-linked

A large majority of the affected persons have been healthy, and there is no evidence that there is any unusual tendency to disease in these families. Many of them have had members who were tuberculous, but this may be accounted for by the ubiquity of this malady, and by the fact that the anomaly is more likely to be detected in the case of tuberculous patients in sanatoria, because of the periodical examinations of the blood which are made there. The Wassermann test has been negative in all of the cases in which it has been done. The association with hyperthyroidism in Peterson's family (5 cases) is unique in the literature.

The occurrence of this anomaly exclusively as an inherited trait indicates that the segmentation of the nuclei of the neutrophils and eosinophils is regulated by a constitutional factor. When this becomes modified by the process of mutation, the anomaly takes place, and is transmitted to the descendants as a dominant character.

Diagnosis The diagnosis can be made from the stained smear by one who is familiar with the condition, on the following points: (1) The even contour and tendency to kidney shape with rounded ends on the part of the nuclei of the staff cells, (2) the failure to find neutrophils with more than two nuclei, and (3) the absence of toxic granulation. In all of these respects the blood picture differs from the infectious shift to the left. In case of doubt the absence of signs of infection in the patient, and investigation of the relatives will clarify the situation. Failure to recognize the condition may lead to a serious mistake in prognosis.

The anomaly might be of medico-legal importance, as regards questions of identity and paternity.

Prognosis From the evidence available, it appears that the health of persons with this anomaly is not adversely affected, and that their leukocytes are adequate so far as function is concerned.

SUMMARY AND CONCLUSIONS

1 A case of familial shift to the left of the leukocytes is reported, in which no other members of the family were found to be affected, probably on account of the lack of direct descendants.

2 The typical blood picture was present, viz., a high percentage of staff cells, mostly of crescentic or kidney shape, absence or extreme rarity of segmented forms with more than two nuclei, even contour of the nuclei, and absence of toxic granulation.

3 The literature is discussed.

The writer extends his thanks to Dr. R. M. Thomas and Prof. George H. Smith for assistance in the blood studies, and to Professor J. G. Dusser de Barenne for translating the Dutch articles.

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CASE REPORTS

TRANSVERSE MYELITIS FOLLOWING MUMPS^{*}

By A C FORTNEY, M D , *Fargo, North Dakota*

ALTHOUGH it is not unusual to find meningitis, encephalitis, neuritis, and delirium as complications of mumps, myelitis is most uncommon. Woltman and McKaig reported such a case in 1933, and at that time a very close search of the literature revealed only one other case, that of Warrington's reported in 1914. However, a third case was reported by Kuligowski in October 1933. I should like to add another to those reported.

CASE REPORT

Mr N E, white male, aged 39, hardware dealer, first contracted mumps on December 26, 1935. Involvement first appeared in the right parotid, and four days later the left side became swollen. Mild bilateral orchitis developed, but rapidly subsided. His symptoms were mild. Delirium, headache, and neuritis did not appear. He did not feel sick enough to remain in bed longer than two days. On the evening of January 6, 1936, twelve days after the onset of the mumps he first noticed a little tingling in the soles of both feet. He had had no headache nor any pain in the neck or back. By the afternoon of January 8 his legs were so weak that he had to hang onto chairs or the wall to keep from falling down. By this time the tingling in the soles of the feet and legs had given away to a numb feeling. At this time, it had been 16 hours since he had urinated, and 24 hours since his bowels had moved. In spite of this he had neither the desire to urinate or defecate, nor did he experience any pain in the region of the bladder. Large doses of patent cathartics failed to move his bowels.

The next morning, January 9, his family physician was called who catheterized him, and obtained a large amount of urine which was not measured. A large soapy enema was given but had to be siphoned off as the patient was unable to expel it. His temperature was 100° F, pulse 84 and white blood cells 10,500. The patient was then moved to a hospital, where I saw him in consultation with Dr O S Crause of Towner, North Dakota, on January 10. A spinal puncture on admission revealed clear fluid under normal pressure. Five cells were counted and there was a trace of globulin.

Past History He had never had mumps until the present attack. He had had the other usual childhood diseases without any complications. He had had no serious illnesses, injuries, or operations.

Family History Father died of arteriosclerosis. Mother living and well. Three brothers are living and well. No history of cancer, tuberculosis, diabetes, or insanity.

Physical Examination The patient was a well developed and nourished white male of apparent age lying quietly in bed in no distress. The respirations are free and easy, cyanosis is absent and orientation is normal. The entire physical examination except as related to the nervous system is negative.

* Received for publication February 26, 1937.

From the Department of Internal Medicine, Hanna, Clay and Lancaster Clinic, Fargo, N. Dak.

Neurological Examination The pupils are equal and regular and respond normally to light and accommodation. The fundi are normal. Extra ocular movements are normal. The patient has noticed no diplopia. The ears are normal, and hearing as tested with a watch is normal for both ears. There is no demonstrable weakness of the facial muscles. Sensation to pin prick, cotton, heat and cold over the face, neck, and scalp is intact. The tongue protrudes in a straight line and the gag reflex is present. There is no difficulty in swallowing water or solid foods. There is no weakness of the sternocleidomastoid muscles. There is slight rigidity of the muscles of the neck to anterior flexion. There is no swelling of the parotid glands.

Sensation, motor power, and reflexes are normal in the upper right extremity. There is a slight but definite weakness of the entire upper left extremity to all movements. The biceps and triceps reflexes are hyperactive. Sensation to pain, light, touch and temperature changes is slightly impaired in this member.

At the level of the third rib, diminution of sensation to pain, light touch and temperature begins to appear. From the level of the fifth rib and downward, these sensations are completely lost. The abdominal and cremasteric reflexes are absent. On auscultation of the abdomen, peristalsis is noted, and seems to be of normal intensity.

Both lower extremities are completely flaccid, and all superficial sensation is lost. Deep sensation is present. The patellar and ankle reflexes are weak. Patellar and ankle clonus is absent. There is bilateral positive Babinski and Oppenheim. On the right, position sense for the toes is normal, but erratic on the left. There is complete loss of bladder control. The rectal sphincter is toneless and the rectum remains widely opened after digital examination.

A spinal puncture was performed without anesthesia, the patient being aware only of a pressing feeling in the back. The fluid was clear and under 10 mm of mercury pressure. On jugular compression the pressure promptly rose to 24 mm and when released, promptly fell to its original level. Fifteen cc of the fluid were removed and the neck rigidity which was previously noted completely disappeared.

A diagnosis of transverse myelitis, probably due to the virus of epidemic parotitis, was made. It was felt that the outcome depended entirely upon the degree of permanent damage to the cord which only time would tell. It was further felt that cystitis and possibly pyelitis would result from the frequent catheterizations, and that this factor would be the most important in determining whether or not the patient would survive. Absolute bed rest, abstinence from any passive manipulations until improvement began, and splinting of flaccid extremities were ordered. Rigid attention to the care of the skin was emphasized. No medication was ordered except that necessary for intermittent alkalinization and acidification of the urine.

Progress In the next few days the left arm became practically useless and flaccid. Following this there was very little change in the patient's condition up to the time he was discharged from the Hospital, on February 13, 1936. The only sign of return of function at that time was the ability to move the great toe on the right foot. The hospital regime was continued at home and gradual improvement began.

I next saw him on May 3, 1936. At the time he was in the best of spirits, and thoroughly convinced that he was going to get well. Power in the left upper extremity was now comparable to that of the right. He was able to come to a sitting position in bed without any assistance. The abdominal reflexes and cremasteric reflexes were sluggish. A rounded, rather tense, painful mass appeared above the symphysis to a point half way to the umbilicus. This was a distended bladder. The patient was able to move in any direction in bed without aid. However, on determining the strength passively in his legs it was still found to be much diminished, in the left more so than in the right. Astereognosis and adiadokokinesis were absent. Position sense of the toes was normal. Sensation to pin pricks, cotton, and tem-

perature changes was practically normal over the entire body. A specimen of urine was bloody. Patient was having a definite overflow type of urination, and was still being catheterized daily. It was evident that a severe cystitis was present. The temperature showed daily fluctuations, going as high as 100.5° F.

The remainder of the physical examination was normal. At that time it was evident that the patient was making very satisfactory progress in every way except in regard to the urinary tract infection. The risk of a general infection was still a definite one. In July 1936, he returned to the Hospital and a cystotomy with supra pubic drainage was done. Since then his urinary infection has cleared up considerably and now he has complete control of the bladder and bowels. He is able to walk around with practically no difficulty. The patient may be classified as a completely recovered case.

SUMMARY

A case of myelitis following mumps is presented. The rarity of the entity is made note of, there being only three other cases reported in the available literature. This case corresponds very closely as to time of onset, symptoms and clinical findings to those reported by Woltman, Warrington and Kuligowski except for the absence of back pains.

The prognosis in this type of complications must be guarded. In the four cases reported, one died on the ninth day of illness, one showed no improvement 19 months after onset, one was completely well at the end of eight weeks, and the case reported here showed complete recovery at the end of seven months. Only conservative treatment was instituted. However, the use of convalescent serum intra-spinaly and intra-venously and the employment of frequent spinal puncture might well be given a trial in such instances of spinal cord involvement following mumps.

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INTERNAL HYDROCEPHALUS FOLLOWING REPEATED INTRAVENTRICULAR HEMORRHAGES *

By FRANCIS J. SCULLY, M.D., F.A.C.P., *Hot Springs, Arkansas*

SPONTANEOUS intraventricular hemorrhage is quite rare and when it occurs is usually promptly fatal. A recurrence of such a hemorrhage is therefore quite unusual. The following case is especially interesting because of the development of an extensive internal hydrocephalus following repeated intraventricular hemorrhages.

CASE REPORT

Mrs. J. S., aged 60, was seen in consultation with Dr. H. A. Ross of Arkadelphia on November 1, on account of a persistent headache and dizziness. On October 16

* Received for publication August 24, 1936

the patient had suddenly dropped over unconscious while sewing. She had previously felt well, and that morning had eaten breakfast as usual. She remained comatose for about 15 minutes. Following this attack she had developed headache, which gradually became more severe and had continued since. She required morphine, bromides, and amytal to keep her comfortable. The headache was persistent and extended down into the back of the neck. For three days there was rather marked vomiting and the vision became blurred. These symptoms had shown improvement until on October 31, when she had two mild convulsive attacks with some movement of the right arm over the chest. At the onset of the illness the blood pressure was 180 mm of Hg systolic.

The patient had had influenza five years before. A panhysterectomy had been performed 20 years before on account of a tumor of the uterus, which was thought to be cancerous. She had borne six children, five of whom are living.

Examination showed the patient to be rather pale and in a semi-stupor. The heart and lungs were normal. Blood pressure 160 systolic and 80 diastolic, pulse 60, temperature 98.4° F. The peripheral vessels showed a moderate sclerosis. The pupils were small and equal, and reacted only slightly to direct light due to opiates. Ophthalmoscopic examination showed a choking of both discs. The tongue was extruded in the midline. The deep reflexes were active and there was no paralysis or sensory changes in the extremities.

Laboratory tests showed hemoglobin 60 per cent, red blood cells 3,280,000, and white blood cells 10,100. The Wassermann test was negative on both the blood and the spinal fluid. The spinal puncture yielded fluid under increased pressure, showing a heavy trace of globulin and many red blood cells. The fluid was of a golden yellow color, but did not clot on standing.

From these findings it was thought the patient had a brain tumor in which a hemorrhage had occurred, and that the convulsive attacks had appeared during the period of active bleeding. Since there were no localizing symptoms, and since there had been a period of recovery after the first hemorrhage, it was thought best to keep her quiet in bed and to use sufficient sedatives to control the discomfort, in the hope that the bleeding would subside and that immediate surgical intervention would not be required.

During the month of November the patient improved. There were several mild attacks but no stupor following them. There was improvement in the vision and when seen by Dr. O. H. King, on November 20, the eye grounds were normal.

On December 2 the patient had a severe convulsive attack, with gradually increasing stupor, which continued until she died.

Autopsy. The brain was removed and examined by Dr. D. C. Lee, who reported that on section the brain showed a marked internal hydrocephalus. The lateral ventricles were markedly dilated and the septum between them was obliterated. The third and fourth ventricles were also dilated. All the ventricles were filled with clotted blood. There was some blood extending out from the fourth ventricle on the base of the cerebellum. The corpus callosum was very much thinned and the dilated ventricles measured 10 by 5 cm. at the base of the anterior horn. In the anterior horn of the right lateral ventricle there was a spongy mass about 4 cm. long and 2 cm. wide. It was attached loosely to the inner and lower wall of the ventricle at the anterior portion of the choroid plexus. No tumor mass could be found. On microscopic examination the mass proved to be an organized blood clot, with a number of dilated vessels of the choroid plexus included.

DISCUSSION

From the pathological findings it was evident that this patient had had repeated hemorrhages from the anterior portion of the choroid plexus in the right

lateral ventricle and that the bleeding had been sufficient each time to fill the ventricles with blood causing an internal hydrocephalus. The blood pressure was above normal which made the hemorrhage more likely to occur. The convulsive attacks occurred with each repeated hemorrhage. When the spinal puncture was made in November the golden yellow color was due to the previous hemorrhage, and the red cells found were probably due to the hemorrhage that had occurred the day before. With each hemorrhage there would be sufficient pressure on the brain to produce the convulsion, and to cause the interference with vision which was noted. With the absorption of the blood these symptoms would subside. The organized clot of blood was a further indication of the repeated hemorrhage and of the attempt of the body to control the bleeding. The last hemorrhage was so marked that the vital centers of the brain were too depressed for the individual to survive.

Intraventricular hemorrhage is not uncommon in severe traumatic injuries to the head and brain. In newborn infants it also occurs more often than is generally suspected. Hemsath¹ reports its occurrence in 4.8 per cent of a series of 414 autopsies of still born and newborn infants. Occasionally in massive cerebral hemorrhages the bleeding will extend from the internal capsule into the ventricle.

Spontaneous intraventricular hemorrhage having its origin in the ventricle is quite rare. Copeland² reports one case in a man, aged 51, with arteriosclerosis and hypertension. The hemorrhage had its origin in the walls of the aqueduct. Sands and Lederer³ reported three cases, two with arteriosclerosis, and one with intracranial aneurysm. They state that the diagnosis of intraventricular hemorrhage is very difficult even under the most ideal conditions. A good review of the symptoms in these cases is given in their article.

Apparently intraventricular tumors do not give rise to hemorrhage as often as one would suppose. Dandy,⁴ in 1933, reported 13 cases of benign tumors in the ventricle, and reviewed 25 additional cases from the literature. In one of his cases a venous aneurysm in the wall of the ventricle was removed after a second hemorrhage had occurred in the right ventricle. Eight additional cases were reported in 1934 by Fincher,⁵ but none of them were accompanied by hemorrhage.

In the case reported above it was not possible to determine whether there was an aneurysm of the vessels of the choroid plexus at the point where the hemorrhage occurred. On microscopic section it was noted that the vessels were very thin and dilated where they were a part of the organized clot of blood. It is possible that these thin vessels had ruptured with some sudden increase of the blood pressure, which was already high, and that the clot which formed was not sufficient to prevent subsequent bleeding.

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EDITORIAL

CERTAIN TOXIC EFFECTS OF SULFANILAMIDE

Many men in the past months have likened in their minds the present era in the treatment of infections to that period of excitement which immediately followed the first clinical use of Ehrlich's "606". Indeed many have felt that in the new drug, sulfanilamide, the medical profession had obtained a therapeutic agent of greater importance to humanity than even salvarsan itself.

So chastened are many medical men as a result of repeated chemo-therapeutic disappointments that the earlier announcements of the striking influence of this drug on certain coccal infections were met with a certain degree of cynicism. A larger number, however, not only readily accepted the value of the drug in streptococcal infections but, forgetful of the bitter lessons of cinchophen, amidopyrine, and dinitrophenol, promptly hastened to try the drug in every conceivable condition without heed of possible danger. The therapeutic reports already at hand must convince the most skeptical of the undoubted value of this potent new remedy. It is almost breath-taking to read of the results obtained in such highly fatal conditions as streptococcus meningitis, streptococcus septicemia, puerperal fever and in meningococcus meningitis. On the other hand there is no doubt that the drug exhibits toxic effects and that in some cases these may be of a serious nature. There is a wealth of recent reports on these toxic manifestations. It is important, therefore, for every man in the practice of medicine to be able to weigh carefully the relative advantages and disadvantages of the employment of this drug.

Whatever is written concerning the subject of sulfanilamide today may well be out-dated or contradicted by the contents of next month's medical journals, but at the moment it would seem that while there is a highly varied set of toxic manifestations which may follow the use of this chemo-therapeutic agent, yet on the whole we have reason to think that for the most part they are minor in nature and that even those of a more threatening type can apparently be successfully combated. It must be borne in mind, however, that for the most part reports have dealt with the immediately acute effects of the drug resulting from short courses of its administration. Whether, later, more serious injuries may be reported as a result of its prolonged use, or whether delayed reactions may become manifest at a later period in those who have apparently utilized it without harm, remains to be seen.

A great deal of interest is attached to those toxic effects involving the skin. Not far from one in twenty of the patients receiving this drug develop a rash. The most usual form of eruption resembles measles rather closely, there may be mild constitutional symptoms, fever and malaise,

accompanying its appearance. The rash is most apt to occur after the drug has been taken for five days or more. It disappears fairly promptly upon discontinuance of the sulfanilamide but may recur if more of the drug is taken. Recently an interesting observation has been made by several authors^{1, 2, 3} that a more violent form of eruption may occur in those who have been taking this drug, over such areas of the body as are exposed to sunlight. In certain of these cases there has been a marked swelling of the affected part, edema and infiltration of the skin, and large coalescent macules and papules of a pink to dusky red color. The skin condition may progress to a marked vesiculation. In convalescence it is followed by desquamation. With the onset of this severe eruption, there may be quite marked nausea, chills and fever. The nature of the photosensitivity in these cases has not been further investigated.

Cyanosis is very common in those taking the drug and its intensity is often quite alarming. There is still a great deal of confusion as to the nature of this abnormal coloration. Some have attributed it to the presence of methemoglobin, others to sulphemoglobin, but equally careful observers have been unable to find evidence of either of these forms of hemoglobin and they are inclined to believe that in certain instances, at least, there is a new abnormal compound formed in the blood which gives it its cyanotic color. The cyanosis is not accompanied by any evidence of distress on the patient's part and when because of the seriousness of the infection, the drug has been continued regardless of the patient's color no apparently harmful consequences have followed.

It has been discovered⁴ that slight degrees of acidosis, as determined by a lowering of the CO₂ combining power of the blood, are present in a considerable proportion of patients taking sulfanilamide. Since in a few cases the degree of acidosis has been quite severe, it has been recommended that 10 grains of sodium bicarbonate be given with each dose of sulfanilamide.

Among the most striking and serious of the toxic effects which have been so far observed are those involving disturbance of the normal blood picture. Slight grades of anemia have been frequently noted, apparently as a consequence of full doses of the drug. Quite different, however, are the cases of acute hemolytic anemia^{5, 6} which may come on very suddenly in patients taking routine dosages of this new remedy. Pallor, profound weakness, and

¹ MENVILLE, J. G., and ARCHINARD, J. J. Skin eruptions in patients receiving sulfanilamide, *Jr Am Med Assoc*, 1937, cix, 1008.

² GOODMAN, M. H., and LEVY, C. S. Eruption during administration of sulfanilamide, *Jr Am Med Assoc*, 1937, cix, 1009.

³ FRANK, L. J. Dermatitis from sulfanilamide, *Jr Am Med Assoc*, 1937, cix, 1011.

⁴ SOUTHWORTH, H. Acidosis associated with the administration of para-aminobenzene-sulfonamide (Prontylin), *Proc Soc Exper Biol and Med*, 1937, xxvi, 58-61.

⁵ HARVEY, A. M., and JANEWAY, C. A. Development of acute hemolytic anemia during administration of sulfanilamide, *Jr Am Med Assoc*, 1937, cix, 12.

⁶ KOHN, S. E. Acute hemolytic anemia during treatment with sulfanilamide, *Jr Am Med Assoc*, 1937, cix, 1005.

jaundice accompany the rapid fall in the red count. If the process is severe, the blood serum may be port wine color from the liberated hemoglobin and the urine a dark brown from hemoglobinuria. In a case recently seen the red count fell from 4.5 million to 700,000 in less than two days. Fortunately, cessation of the drug is apparently followed at once by cessation of the hemolytic process. Transfusions are very helpful in tiding the patient over the acute phase of the process. Cases observed so far have all recovered.

There has been a great deal of fear from the start that the drug might cause granulocytopenia. There have been a few undoubted cases and in one at least of these death was attributed to this complication of treatment. However, in most of the relatively few cases so far reported recovery has been prompt upon removal of the drug.

Patients taking the drug very usually notice some slight general symptoms of the nature of dizziness, slight headache and ringing in the ears. These may safely be ignored. More serious neurological effects such as have been described in experimental animals have not appeared in man. An exception to this rule is the case of a patient recently reported⁷ who developed a toxic optic neuritis with severe temporary loss of vision. Fortunately, the recovery of this patient is apparently going to be complete.

It is well, of course, for the physician who contemplates using this drug to be aware of the nature of the toxic effects which may be produced. In certain instances these effects seem to be dependent to some extent upon the size of the dosage and the length of time it had been employed. There is some evidence that this is particularly true of the skin eruptions. On the other hand, the acute hemolytic anemia and the granulocytopenia appear to be due to idiosyncrasy. They may appear on normal dosage within the first few days after the drug has been started. It is not likely then that the occurrence of a certain percentage of these cases can be avoided.

It is believed that the use of sulfates, such as magnesium sulfate and ferrous sulfate simultaneously taken with sulfanilamide, predisposes to the formation of sulphemoglobin and perhaps to other complications. It has been suggested that paraldehyd diminishes the efficacy of the drug. A safe rule would be to avoid concurrent therapy with other medicinal preparations if this is feasible. The physician should recall too that sulfanilamide is excreted almost entirely through the kidney. When the renal apparatus is normal excretion of the drug is fairly rapid, and it is this rapid excretion, no doubt, which tends to cut short the toxic manifestations as soon as the intake of the drug is discontinued. On this account, however, the giving of the drug to a patient with chronic or acute nephritis carries with it a hazard that if toxic effects occur, they will perhaps be more prolonged and more serious than in the patient with normal excretory powers. It is certainly the part of caution also, that during the course of administration of

⁷ Bucy, P. C. Toxic optic neuritis resulting from sulfanilamide, Jr. Am. Med. Assoc. 1937, civ, 1007.

the drug, the patient should be kept at rest and under daily observation. It would be a wise rule also to warn all patients not to expose themselves to strong direct sunlight.

As in the case of all new remedies the physician is called upon to balance carefully in his mind the importance of the advantage to be gained by the use of the drug against the possible disadvantages of its as yet only partially known toxic effects. The conservative physician will not use this powerful remedy unless he is faced with a disease of dangerous character not equally amenable to other forms of treatment.

M C P

REVIEWS

To Drink or Not to Drink By CHARLES H. DURTEE Longmans, Green and Co., New York 1937 Price, \$1.00

This interesting and lucid book on the problem drinker deals with but one aspect of the chronic alcoholic problem. The author does not undertake to discuss those diverse pathological mental problems associated with or proximal to chronic alcoholism.

The book consists of 11 chapters, the last being an epilogue on the archaic attitude of the general public towards alcoholism. The popular attitude towards the chronic alcoholic has been to condemn and to make a moral issue. This popular conception, with its indignant attitude and vindictive outlook, stands in paradoxical relationship to the opinions of poets and philosophers who have sung of the joys of drinking down through the ages. These two paradoxical attitudes are broadly but forms of individual rationalization and probably bear a relation to the popular concepts respecting individual responsibilities involving choice of behavior. The author implies, however, that this popular concept must be replaced with a more scientific one of natural phenomena being an endless chain of cause and effect.

It is not possible to understand the nature and causes of wickedness, of the bad and the sordid, or the mean and the vile, or the abandonment of all those things by which men ordinarily live, if the approach is in the direction of intolerance and condemnation for alcoholism. The problem drinker cannot be understood, satisfactorily treated, or his condition ameliorated or prevented through an emotional outlook that is influenced by a spirit of vindictiveness or maudlin sympathy. With the above premise in mind the theme of this volume is perhaps expressed in the author's own words, thus, "Modern therapy of alcoholism takes its stand on practical grounds. Its effort to change conduct, unlike the miracle methods of old, are based on the hypothesis, confirmed by both research and common sense, that the behavior of an individual is the interaction of himself and his circumstances. If we recognize alcoholism as a symptom of some difficulty of the whole man and deal with it realistically we rob it of its terrors and offer freedom and happiness to countless harassed problem drinkers."

The volume is vouched for in a signed foreword by Dr. Arthur Ruggles, Superintendent of Butler Hospital, Providence, Rhode Island, who comments that the methods of approach to the problem drinker as outlined by the author are superior in many respects to those previously prevailing.

The author expresses the hope that the book may be of value to the family physician, the clergyman, the welfare worker and the public administrator, and all who come in contact with the drink problem. It is obvious that many family physicians are consulted from time to time concerning the best methods of approaching the problem drinker who is detrimental to himself and those nearest and dearest to him. In the use of this little book serious consideration might be given to the possibility of its being placed on the family physician's reading list for prescription to the problem drinker and those who come in contact with him, since the book affords many passages to stimulate reflection for the problem drinker to better know himself.

In analyzing the theme of this publication one somehow automatically turns to the writings of that great humanitarian, Charles Dickens, who said, "Who turns his back upon the fallen and disfigured of his kind, abandons them as vile, and does not trace and track with pitying eyes the unfenced precipice by which they fell from good, does wrong to Heaven and man, to time and to eternity."

W L T

The Diagnosis and Treatment of Diseases of the Stomach and Intestines By WILLIAM FITCH CHENEY, B.L., M.D. 378 pages, 15.5 × 24 cm Oxford University Press, New York 1936 Price, \$5.50

This volume is one of the Oxford series of "Monographs on Diagnosis and Treatment" The author has attempted to present the subject of the diseases and disturbances of the gastrointestinal tract in sufficient detail for practical use and still to avoid lengthy theoretical discussion Certain subjects of interest to the specialist are necessarily omitted The treatise is based on the author's own experience and contains very few references to the literature but the occasional authority to whom attention is called shows clearly that the volume is up to date Moreover, the discussions of gastroscopy and gastrophotography give the same impression

The book is divided into two parts, one devoted to "Diseases of the Stomach," and the other to "Diseases of the Intestines" Both parts are developed according to the same plan so that the second half of the volume, with certain exceptions, is a counterpart of the first Throughout the volume the discussions are clear and concise Case reports are presented briefly and so effectively that they may be said to illustrate the text

Although the volume contains all the essential data necessary in the modern study and treatment of gastrointestinal disease it nevertheless is not a satisfactory reference book for the specialist It probably was not meant to be Furthermore, although it avoids controversy the writer's conviction that gastroparesis is associated many times with disturbances of digestion and that correcting the former removes the latter may be responsible for a good deal of debate

By succinctly presenting the diseases under discussion and bringing them up to date with regard to diagnosis and treatment and by stressing the care that must be taken in localizing a pathologic change in the proper organ the writer has given us a splendid part of an excellent system of books

S M

Treatment in Psychiatry By OSKAR DIETHELM, M.D. 476 pages, 16 × 24 cm Macmillan Company, New York, N.Y. 1936 Price, \$4.00

There are so remarkably few volumes devoted to the treatment of the mental disorders that such a one is very welcome It is carefully and thoughtfully written It is fundamentally sound

It begins with a study of personality, followed by general principles of treatment, then proceeds to an exposition of suggestive and hypnotic procedures, psychoanalytic procedure, and the special psychotherapeutic variations of Adler, Jung, Trigant-Burrow, Rank and Stekel, Du Bois, and Kronfeld, as well as the indirect methods represented by association experiments and Rorschach's Tests

Dr Diethelm then presents his own general views (and those of Dr Adolph Meyer's followers) in a chapter called Distributive Analysis and Synthesis

The rest of the book consists of detailed examination of what he feels to be the primary considerations to be dealt with in each type of disorder He tells how he handles these problems as they arise and illustrates with pertinent and well chosen case history briefs

The whole presentation seems to us distinctly on the dogmatic side In a work of this kind this is not a bad fault since it is designed to be used by physicians in general, who may not be too familiar with the diversity of views held by professional psychiatrists, but who are looking for concrete treatment programs to follow

We feel it does not adequately stress the enormous therapeutic value of the simple rapport or physician-patient fellow-feeling relationship which leads to many recoveries regardless of any technics It lays much too much stress on the use

of drugs, particularly sedatives. Here they would seem to hold a prominent if not preeminent place in every treatment program. They do have their usefulness—in selected cases—but we would have preferred to see the author sound a note of caution in their use.

We have always been curious as to the reasons why hypnosis receives as much attention as it always seems to, in view of the fact it is now so little used.

This book will naturally be of much more use to the psychiatrist than to physicians outside this especial field, but is probably the best treatment text in English which has so far appeared.

H M M

Clinical Allergy By LOUIS TUFT, M D 711 pages, 24 × 15½ cm W B Saunders Co., Philadelphia and London 1937 Price, \$8 00

This book is an eminently satisfactory manual of practical allergy. It should be useful to the general practitioner and student and, in addition, should prove of value as a manual of practical procedures for allergists and for technicians connected with allergy clinics.

Dr Tuft, while giving the background of the subject and presenting the important points of its development together with the various views held, on different phases of the subject, is sufficiently dogmatic to make the text workable as a practical guide.

The arrangement of the book is quite satisfactory. He first considers the general principles involved, explaining the mechanism of anaphylaxis and allergy and giving the general principles of diagnostic and therapeutic methods. He next considers allergic conditions from an etiological standpoint. Under this section he discusses serum, drug, food, pollen, bacterial and physical allergy. The third section considers allergy from the standpoint of its clinical manifestations, taking up asthma, allergic rhinitis, gastrointestinal allergy and migraine.

His fourth section, which is called Allergic Dermatoses and Allergy in Relation to the Specialties should be most valuable to men in other fields, especially those interested in nose and throat diseases.

Not the least important portion of the book is the appendix. Here, Dr Tuft covers the laboratory methods in anaphylaxis and in allergy, describing under the latter the passive transfer method of Prausnitz-Kustner, the preparation of liquid and dry allergenic extracts and the preparation of pollens for microscopic examination. He also gives practical, detailed directions for asthma and hay-fever patients. A very valuable feature is the list of the possible allergens in household materials and in foods, together with a list of allergens and their sources. There are allergic diets and recipes which should be most helpful and his bibliography should prove very valuable to anyone interested in the subject.

The book contains a moderate sized but valuable group of pictures. The author has avoided the inclusion of useless photographs which so frequently appear in texts of this sort.

A novel and valuable feature is the use of case vignettes to demonstrate and clarify clinical points under discussion.

The excellent section on pollen allergy leans heavily upon the work of Thommens (Coca, Walzer and Thommens "Asthma and Hay-Fever in Theory and Practice") and the chapter on pollens written by O C Durham for Feinberg's "Allergy in General Practice."

In the opinion of this reviewer, Dr Tuft's book is the most practical one so far written on the subject of allergy and should be of the greatest possible value to anyone interested in this field.

H M B

Syphilis Sive Morbus Humani By CHARLES S. BUTLER 137 pages, $23\frac{1}{2} \times 15$ cm
The Science Press Printing Company, Lancaster, Pa 1936 Price, \$3.00

This small volume has been written by the author as a summary of the evidence indicating, first, that syphilis was present in Europe long before Columbus and hence did not arise in America, and, second, that syphilis and yaws are different manifestations of the same disease. The results of prolonged historical research are evident on every page and the reader will be delighted by many picturesque quotations. The author's interest in his subject overflows into many allied fields so that topics such as the history of slavery are dealt with under sub-headings, and these diversions are almost always very interesting. Altogether the non-specialized reader will find enjoyment and profit in the reading of this little book and will acquire a broader view of the nature of the chief venereal infection.

M C P

COLLEGE NEWS NOTES

GIFTS TO THE COLLEGE

Grateful acknowledgment is made of the receipt of the following donations to the College Library of publications by members

Books

- Dr Charles Solomon (Associate), Brooklyn, N Y—"Formulary of the Jewish Hospital of Brooklyn"
- Dr August A Werner (Fellow), St Louis, Mo—"Endocrinology Clinical Application and Treatment"

Reprints

- Dr Nathan Blumberg (Fellow), Philadelphia, Pa—one reprint, "Bronchiectasis—with Description of the Peri Nasal Method of Introduction of Iodized Oil for Diagnosis and Treatment"
- Dr Milton A Bridges (Fellow), New York, N Y—ten reprints, "The Physician and Modern Dietetics", "Modern Dietetics and the Practitioner", "The Modern Approach to Diet Therapy", "The Primary Contracted Kidney", "Diet Prescription for the Tuberculous", "A Simple Method of Apothecary-Metric Transcription", "Fads and Fallacies Regarding Food and Diet", "Chronic Mucous Colitis", "The Relationship of Precordial Stress, Blood Uric Acid, and Salicylate Therapy", "The Present Status of Nutrition in Relation to Disease"
- Rear Admiral Charles S Butler (MC) U S N (Fellow), Washington, D C—four reprints, "Syphilis Sive Morbus Humanus", "Who Gave the World Syphilis? And How?", "The Importance of the Chancre in the History of Medicine", "A Glance at Results of the 'Last Thirty Centuries' of Venereal-Disease Prevention"
- Dr Anthony C Cipollaro (Associate), New York, N Y—two reprints, "Drug Eruptions", "Electrosurgery in Dermatology"
- Dr Harold G Trimble (Fellow), Oakland, Calif—two reprints, "What Is a Preventorium Child?", "Pneumoperitoneum in Treatment of Pulmonary Tuberculosis"
- Dr Willard R Wirth (Associate), New Orleans, La—one reprint, "Heart Disease and Pregnancy"

New Life Member—Dr Charles W Waddell (Fellow), Fairmont, W Va, by subscription became a Life Member of the American College of Physicians on September 7, 1937

Dr Louis H Fligman (Fellow and Governor for Montana for the College), of Helena, Mont, has been re-appointed a member of the Montana State Board of Health by the Governor of Montana. Dr Fligman has served on the Board since 1919, and acted as President four different times

Under the presidency of Rear Admiral P S Rossiter (Fellow), Surgeon General of the U S Navy, the Association of Military Surgeons of the United States held its Annual Convention in Los Angeles, October 14 to 16

Dr Julius H Hess (Fellow), Dr Robert A Black (Fellow), both of Chicago, and Dr Gerald M Cline (Fellow), Bloomington, Ill, have been named by the Governor of Illinois as members of a newly created Advisory Board of the Division for Handicapped Children, Illinois State Department of Public Welfare

Dr Arthur C Christie (Fellow), Washington, D C, was installed as President of the Fifth International Congress of Radiology at Chicago during September

Dr Charles A Waters (Fellow), Baltimore, was Chairman of one of the sessions on roentgen diagnosis, Dr Albert Soiland (Fellow), Los Angeles, and Dr Arthur U Desjardins (Fellow), Rochester, Minn, were Chairmen of sessions on radiotherapy, Dr George E Pfahler (Fellow), Philadelphia, gave the Caldwell Lecture of the American Roentgen Ray Society on "Treatment of Carcinoma of the Breast" Dr Pfahler also was an honorary vice president of the Congress Dr Benjamin H Orndoff (Fellow), of Chicago, was general secretary

Dr William C Menninger (Fellow), Topeka, Kan, delivered the Rogers Memorial Lecture on "Psychological Factors in Medical and Surgical Conditions" before the 96th annual meeting of the State Medical Society of Wisconsin, held in Milwaukee, September 15 to 17

Dr Logan Clendening (Fellow), Kansas City, Mo, was the banquet speaker at the above meeting, his subject being "The Great Centers of Medical Thought in the Past"

Dr Louis Hamman (Fellow), Baltimore, was one of the speakers in a symposium on non-tuberculous lung conditions at the annual meeting of the Southern Tuberculosis Conference and the Southern Sanatorium Association at Richmond, September 29 to October 1

Dr Edward J Murray (Fellow), Lexington, Ky, was President of the Conference

Dr Francis E Harrington (Fellow), Health Commissioner of Minneapolis, was recently appointed a member of the Hennepin County Sanatorium Commission, to succeed Dr S Marx White (Fellow)

Dr Samuel A Levine (Fellow), Boston, and Dr Cyrus C Sturgis (Fellow), Ann Arbor, Mich, will be guest speakers on the program of the fall clinical congress of the Oklahoma City Clinical Society, November 1 to 4

Dr Edward L Bortz (Fellow), Philadelphia, is Chairman of the Commission on Pneumonia Control of the Medical Society of the State of Pennsylvania

Dr Edward W Bixby (Fellow), Wilkes-Barre, Dr Clifford C Hartman (Fellow) and Dr George J Kastlin (Fellow), Pittsburgh, Dr Leon H Collins, Jr (Associate), Dr T Grier Miller (Fellow), Dr Henry K Mohler (Fellow), Philadelphia, are members of the Commission County medical societies were asked to create pneumonia control committees to be represented at a meeting of the Commission in Philadelphia during early October, when a campaign for the fall and winter was planned Points in the program will be to develop laboratories throughout the State for diagnostic typing and to have the State, in cases properly certified, furnish pneumonia serum to those unable to pay for it

The advisory board of the Pennsylvania State Health Department, at a meeting in July, adopted a regulation making pneumonia a reportable disease

Dr C Walter Clarke (Fellow), New York City, after completing his work with the New York City Department of Health, in the organization of its bureau of social hygiene, has returned to active duty with the American Social Hygiene Association as its Executive Director

Dr LeRoy H Sloan (Fellow), Chicago, has been appointed full Professor of Medicine in the University of Illinois College of Medicine

Dr Cyrus C Sturgis (Fellow), Professor and Head of the Department of Internal Medicine at the University of Michigan Medical School, has been appointed by the Dean to establish a clinic, and to supervise its operation, newly established at the University Hospital, Ann Arbor, through the Rackham Fund \$10,000.00 will be made available annually for a number of years to make a study of rheumatism

Dr John C Ruddock (Fellow), Los Angeles, addressed the 34th annual meeting of the Nevada State Medical Association, during September, on "Peritoneoscopy, Technic and Clinical Experiences"

Dr Warren C Breidenbach (Fellow), Dayton, has been appointed a member of the Ohio Public Health Council

Dr Carl V Weller (Fellow), Professor of Pathology, University of Michigan Medical School, Ann Arbor, delivered a series of postgraduate lectures in Lima, Ohio, September 20 to 24. The subjects included constitutional types in relation to disease, developmental disturbances of the face, mouth and neck, pathology of coronary occlusive disease, the thyroid gland, the gallbladder and the kidneys, parasitic worms of the North Central States, endometriosis, Antony von Leeuwenhoek and his microscopes

Dr Thomas T Sheppard (Associate), Pittsburgh, is a member of the committee appointed to supervise a trust fund of a million dollars given by Miss Emily Renziehausen to the Children's Hospital of Pittsburgh for "Perpetual research in the causes, treatment and cure of diabetes in the youth of the Pittsburgh area"

The first income from the fund is to be used in building an addition to the hospital to be known as the "Renziehausen Memorial Ward and Clinic". In addition to the fund, Miss Renziehausen donated an eleven-acre farm as a site for a home for convalescent children. Any part of the fund not needed for work on diabetes may be devoted to other research work or hospital service

Dr Frank L Roberts (Fellow), Trenton, Tenn, has been given charge of a newly established department of preventive medicine at the University of Tennessee School of Medicine. The department will be jointly supported by the University, the State Department of Health and the Tennessee Valley Authority

Dr Roberts will have the title of Professor of Preventive Medicine. He is a graduate of the University of Minnesota Medical School, 1922, was Health Officer of Gibson County from 1924 to 1928, Director of local health service in West Tennessee for the State Health Department from 1928 to 1930 and Director of Health Demonstrations for the Commonwealth Fund in Gibson County from 1930 to date

Dr Ernest S Mariette (Fellow), Oak Terrace, Minn, Dr J Burns Amberson, Jr (Fellow), New York City, Dr D O N Lindberg (Fellow), Decatur, Ill, and Dr Paul P McCam (Fellow), Sanatorium, N C, participated in the conduct of a symposium on sanatorium administration as a part of the program of the Mississippi Valley Conference on Tuberculosis and the Mississippi Valley Sanatorium Association, Dayton, Ohio, September 22 to 25

OBITUARIES

DR HENRY ROBERT MURRAY LANDIS

Dr Henry Robert Murray Landis (Fellow), a cultured, scholarly citizen and a distinguished, justly celebrated and highly esteemed physician of Philadelphia, died on September 14, 1937

Dr Landis was not only an expert clinician and a much sought after consultant but, in addition, he was a skilled and impressive teacher of medical art, a talented author and a recognized authority upon the diseases of the chest. In recent years Dr Landis has been seriously incapacitated by a chronic, complicated and distressing malady, and his death proved a welcome release from the vicissitudes of an intolerable existence from which the joy of living had long since departed. To those fully aware of the devastating and hopeless illness that he suffered, information that nature's final and infallible panacea, merciful endless sleep, had come to Dr Landis could only be greeted with a sigh of relief.

Dr Landis was known to his intimates as "Bob," "H R M L," or "Hiram," and the number of his admirers, both in and out of the profession, was legion. There will be many a sigh of heartfelt regret from colleagues, friends, patients and former students that such a kind and helpful physician should have become the victim of a relentless and pitiless fate.

H R M Landis was born in Niles, Ohio, in 1872. He was the son of Henry Gardner Landis, M D (1848-1886), who was born in Philadelphia, attended Yale University, where he received an A M degree in 1867, graduated from the Jefferson Medical College in 1870, served as an intern in the Philadelphia General Hospital (Old Blockley), entered practice in Niles, Ohio, and, a few years later, removed to Columbus, Ohio, where he became Professor of Obstetrics in the Starling Medical College. "Bob" Landis spent his childhood in Ohio, but secured his academic training at Amherst College, graduating with Calvin Coolidge in 1894. Following the example of his father, Landis attended the Jefferson Medical College and received his

degree in 1897 Again in his father's professional footsteps, he served his internship at the Philadelphia General Hospital, where he early revealed his talents and capabilities as an investigator, observer, clinician, reporter and literary critic

Dr Landis inherited a love for the best literature and from his school days onward he was recognized as a scholar of distinction The love of literature and the appreciation of the arts proved a wonderful escape from tedious realities when the ill fortune of illness came

At the completion of his internship Dr Landis established his practice in Philadelphia and at once became actively associated with the Medical Department of the Jefferson Medical College and Hospital In this institution Dr Landis came in contact with J Chalmers Da Costa, Hobart A Hare and other physicians who both intellectually and in medical science stimulated and inspired him An active service in the dispensaries supplied his inquiring mind with clinical problems and he found himself busied with both teaching and practice

In 1903 Dr Lawrence F Flick, the Nestor of American workers in the field of tuberculosis, was instrumental in incorporating and directing the Henry Phipps Institute for the Study, Treatment and Prevention of Tuberculosis Dr Landis was fortunate enough to be selected, with Dr Joseph Walsh, to take an active part in directing the studies, clinical and sociological, of this useful and justly celebrated organization

The White Haven Sanitarium for Tuberculosis (Luzerne County, Pa), another organization of Dr Flick's judicious planning, was fortunate enough to enlist the enthusiastic cooperation of Dr Landis, and for thirty years he gave to the patients of this hospital his skilled and efficient services Dr Landis was attending physician to the Department for Tuberculosis of the Philadelphia General Hospital for a number of years and resigned this position only when forced to do so by the stress of other duties When the Henry Phipps Institute became a part of the University of Pennsylvania School of Medicine, Dr Landis became the Director of the Clinical and Sociological Departments At this time, 1912, Dr Landis became the Professor of Clinical Medicine in the University of Pennsylvania School of Medicine, and occupied this position until his death

In 1917, in collaboration with Dr George W Norris, Dr Landis published a textbook, "Physical Diagnosis and Diseases of the Chest" The text, which entered its fifth edition in 1933, has been justly praised as the best single volume upon its subject matter The book is used in scores of medical schools and is a volume that is read alike by student, consultant and general practitioner

Dr Landis was elected to Fellowship in the College of Physicians of Philadelphia in 1904 and has been an active and interested Fellow in all that organization's activities The American College of Physicians elected Dr Landis to Fellowship in 1926 Unfortunately the state of his health prevented Dr Landis from meeting with the Fellows of the College as he would

have enjoyed doing. He was a member of the Association of American Physicians, the American Climatological and Clinical Association, the National Tuberculosis Association, the American Sanitarium Association and many other organizations.

Dr Landis was honored by his Alma Mater, Amherst College, in 1929, by being awarded the honorary degree of Doctor of Science. He is survived by his wife, Margaret Tucker Landis, whom he married in 1902.

The College has lost a distinguished Fellow, the medical world a clinician of exceptional ability and the poverty stricken tuberculous an interested and practical sociologist.

E J G BEARDSLEY, M D , F A C P ,
Governor for Eastern Pennsylvania

DR JOSEPH SAMENFELD

The death of Dr Joseph Samenfeld, of Brooklyn, N Y , occurred abroad on September 5, 1937, at the age of 61 years.

Dr Samenfeld was born in Brooklyn, and after attending public schools, he attended the Pratt Institute and the New York Preparatory School, before entering the University and Bellevue Hospital Medical College from which he graduated in 1903. Dr Samenfeld was for many years Chief of the Medical Clinic of the Jewish Hospital, Assistant, Associate and Attending Physician, St Catherine's Hospital, Attending Physician, Greenpoint Hospital, Consulting Physician, Williamsburg Maternity and Lutheran Hospitals, Member, Kings County Medical Society, New York State Medical Association, Williamsburg Medical Society, the American Medical Association and a Fellow of the American College of Physicians since 1923.

Dr Samenfeld volunteered for service in the World War and was commissioned a captain in the U S Medical Corps. He received a congressional medal for distinguished services. He is survived by a twin brother and six sisters.

The community and the profession have lost in Dr Samenfeld an untiring, diligent worker.

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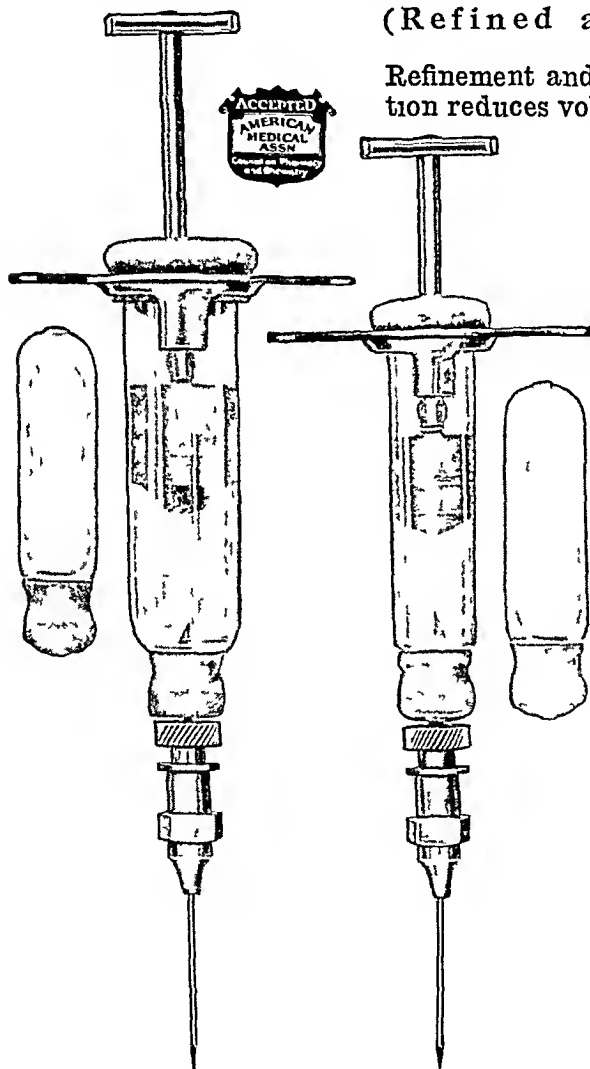
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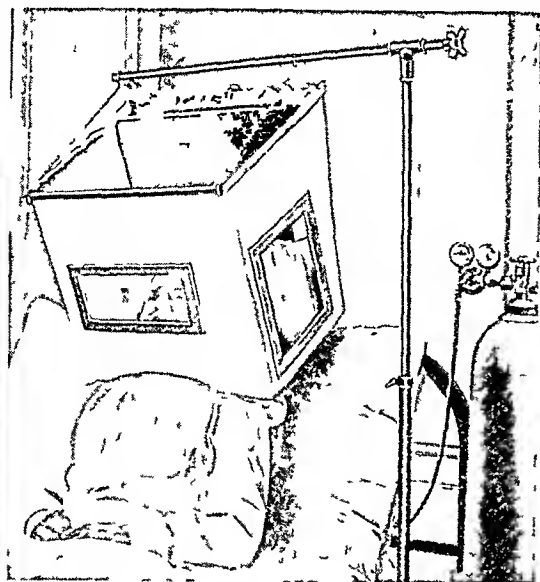
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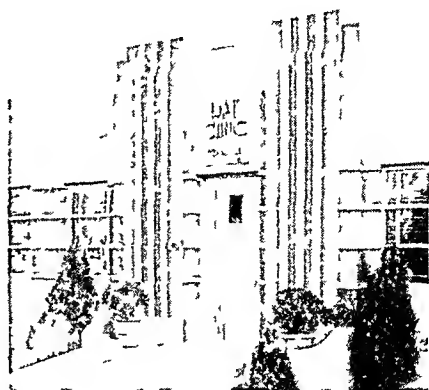
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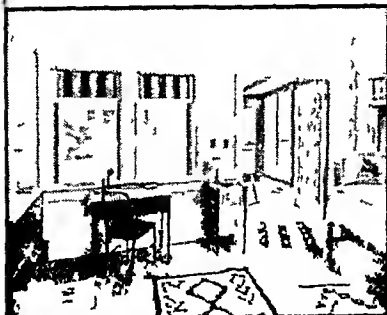
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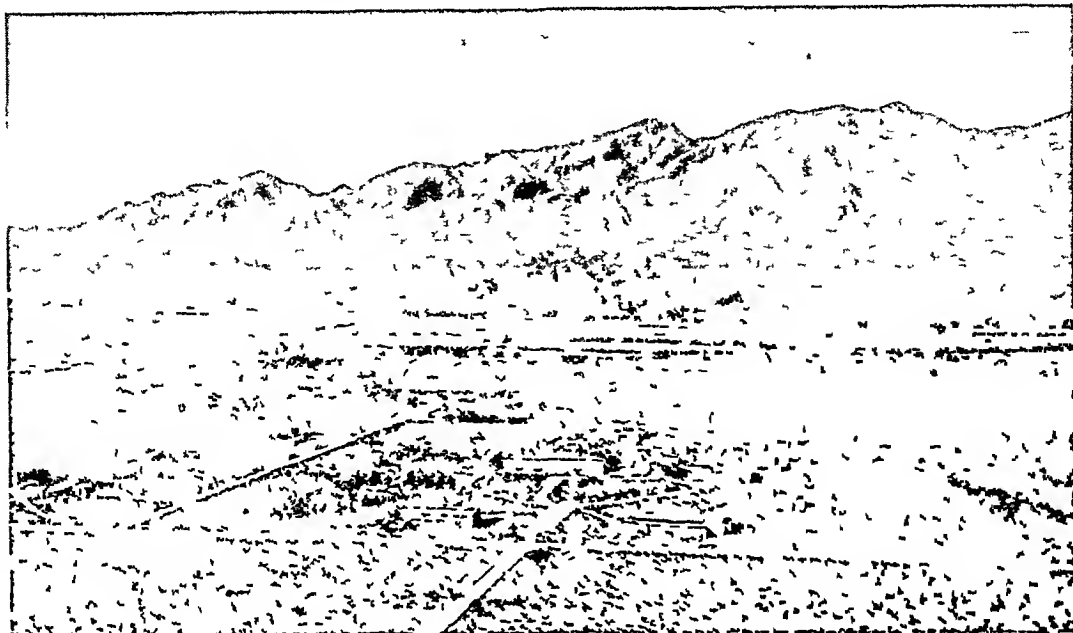


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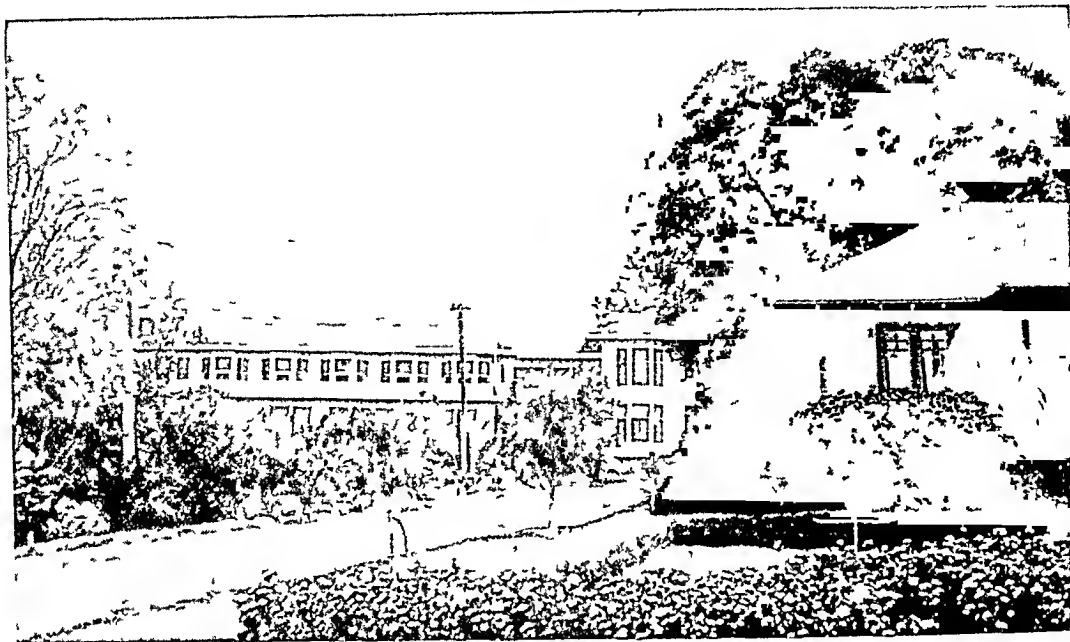
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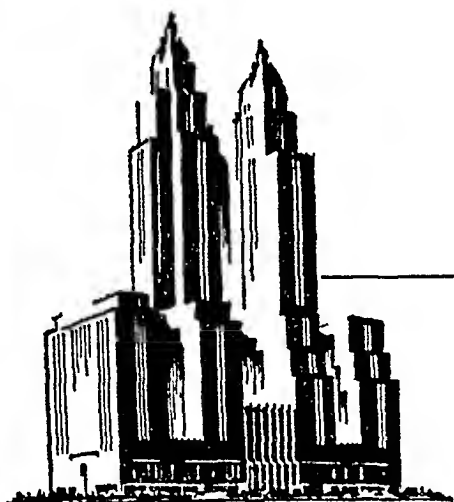
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Place of Publication—Prince and Lemon Sts, Lancaster, Pa

Editorial Office—University Hospital,
Baltimore, Md

Executive Office—4200 Pine Street,
Philadelphia, Pa

THE ANNALS OF INTERNAL MEDICINE is published by the American College of Physicians. The contents consist of contributions in the field of internal medicine, editorials, book reviews, and a section devoted to the affairs of the College.

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ANNALS OF INTERNAL MEDICINE

PUBLISHED BY

The American College of Physicians

VOL. 11 (O S, Vol. XVI)

NOVEMBER, 1937

NUMBER 5

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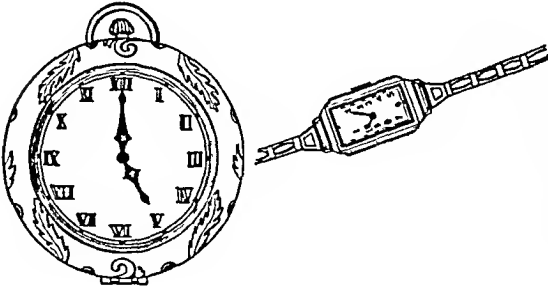
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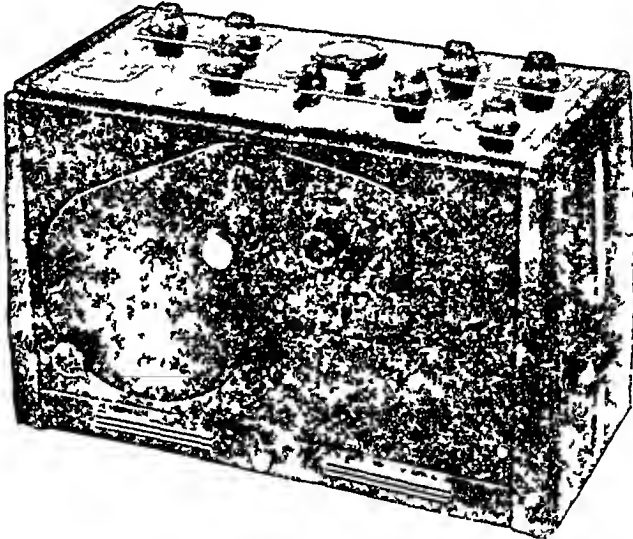
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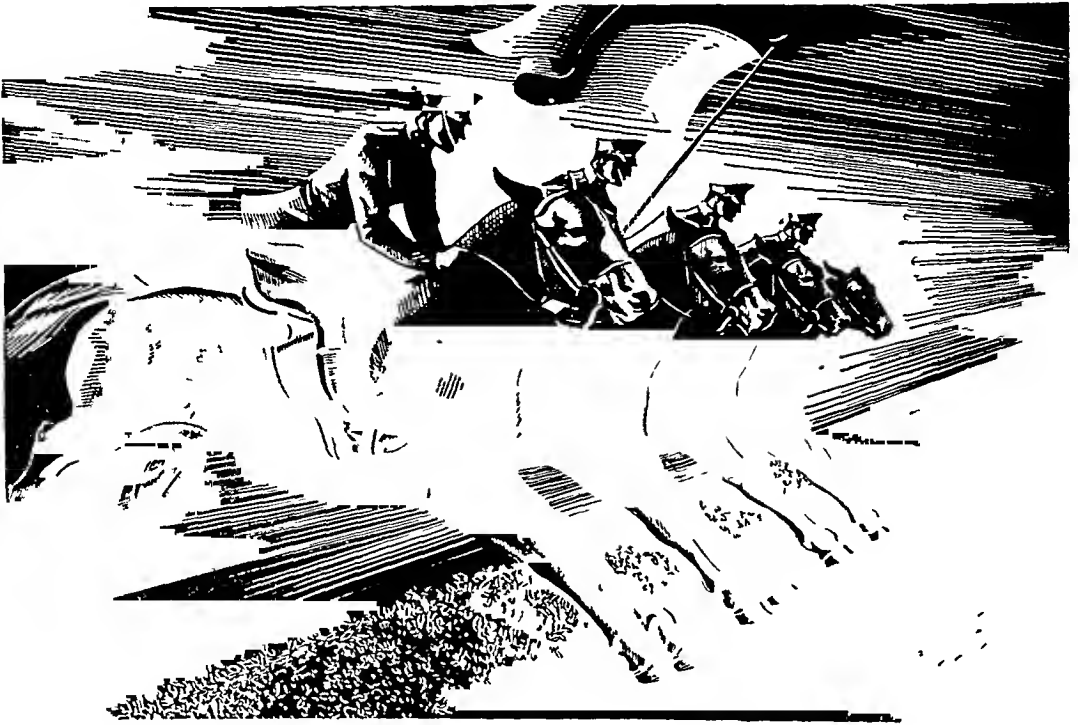
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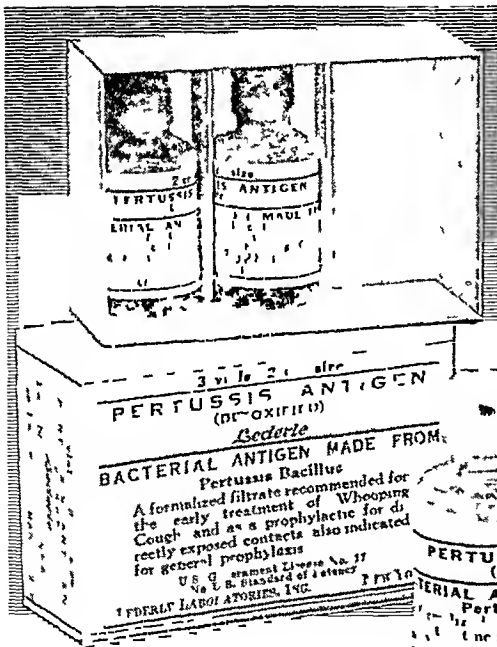
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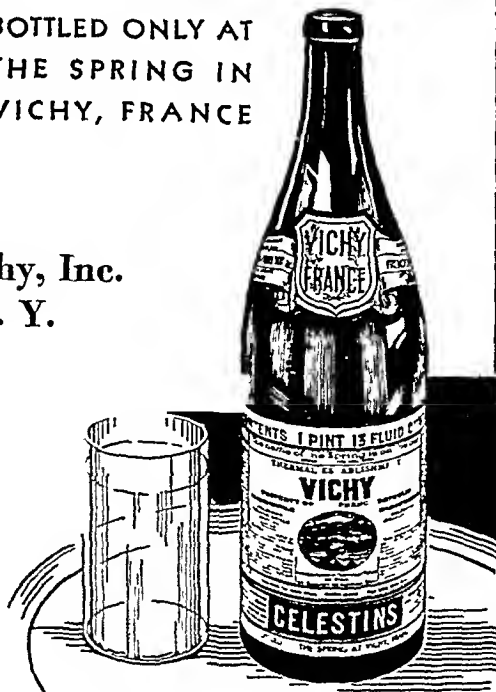
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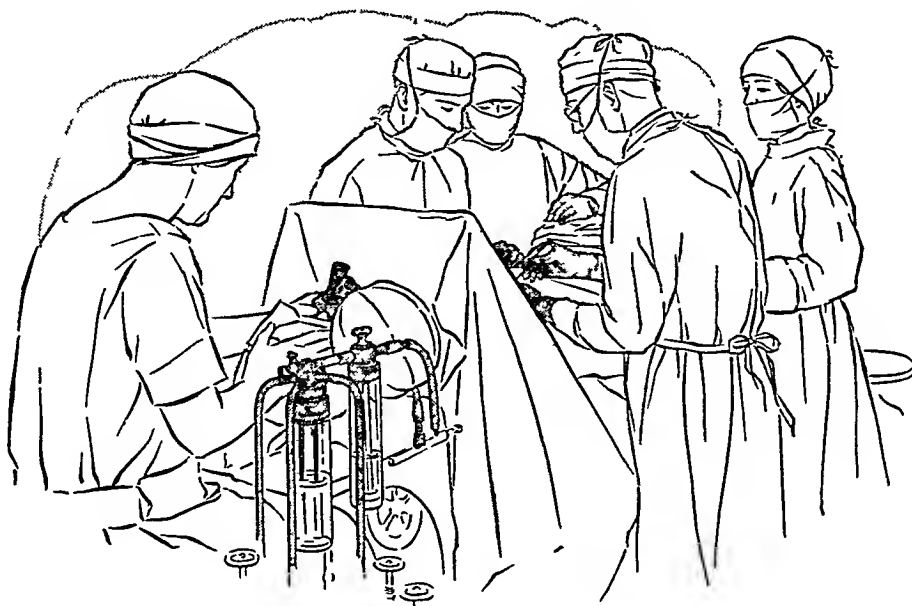
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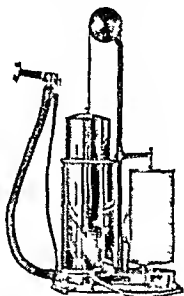
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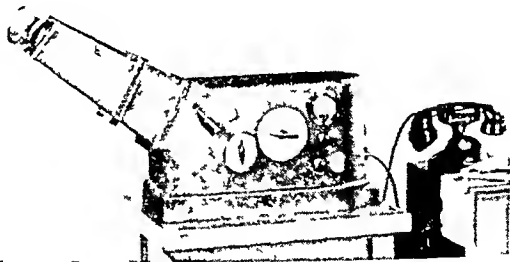
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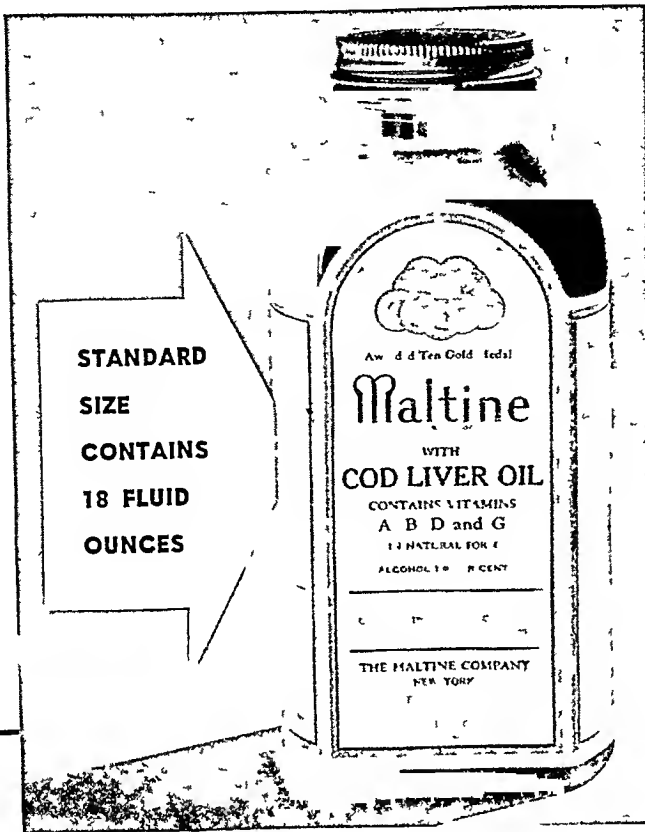
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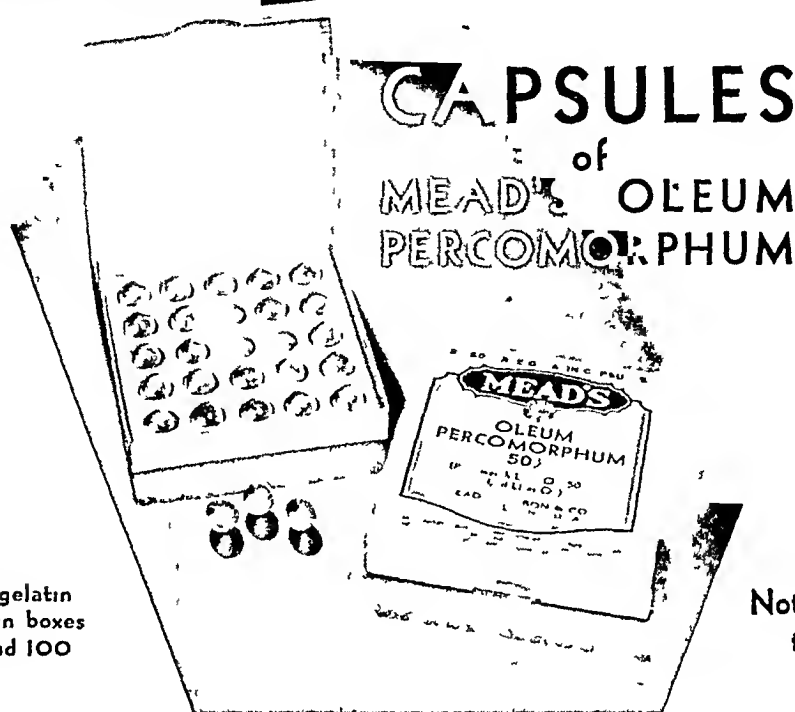


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ANNALS OF INTERNAL MEDICINE

VOLUME 11

NOVEMBER, 1937

NUMBER 5

THYROID-PITUITARY RELATIONSHIP IN DIABETES INSIPIDUS *

By THOMAS FINDLEY, JR, M D, *St Louis, Missouri*

ALTHOUGH it has long seemed reasonable to attribute diabetes insipidus to hypofunction of the posterior pituitary it has, until recently, been difficult to understand why lesions limited to the hypothalamus can establish the condition and why on the other hand experimental hypophysectomy does not. The modern theory of diabetes insipidus, as expressed by Ranson and his collaborators whose own brilliant researches¹⁻⁹ have contributed so much to its conception, goes far toward reconciling such inconsistencies as these and provides at least a working hypothesis susceptible of experimental and clinical demonstration. It rests upon the recent fundamental discovery of a bundle of non-myelinated nerve fibers which arise in various parts of the hypothalamus and descend the pituitary stalk to terminate in the posterior lobe of the hypophysis and also possibly in the intermediate lobe. Detailed accounts of these anatomical studies are contained in the writings of the Chicago group^{1, 2, 4, 6, 7}. Their functional implications are at once apparent when it is seen that a permanent polyuria comparable to diabetes insipidus has been produced in the rat, cat, dog and monkey by bilateral interruption of this so-called hypothalamico-hypophyseal tract, (a) at the supraoptic nuclei¹⁰, (b) along the course of the tract either in the anterior hypothalamus^{1, 2, 4, 11, 12, 13, 14, 15} or in the pituitary stalk^{16, 17, 18, 19, 20}, or (c) in the posterior lobe itself^{16, 21, 22}. That this tract influences the secretory activity of the posterior pituitary is strongly suggested by the facts that experimental injury to the hypothalamic nuclei or to the tract itself is followed by degeneration of the tract distal to the site of trauma,^{2, 10, 17, 23} by atrophy of the posterior lobe (Broers¹⁰ even observed homolateral atrophy after destruction of one supraoptic nucleus), and by a greatly diminished concentration of pressor, oxytocic and antidiuretic material in extracts of the posterior lobe^{7, 8}. Presumably the impulses which reach the posterior lobe from the

* Read at the St. Louis meeting of The American College of Physicians, April 19, 1937.
From the Department of Medicine, Washington University and Barnes Hospital, St. Louis, Mo.

floor of the third ventricle are secretory in nature and this form of polyuria is essentially paralytic rather than irritative in origin since the permanently excessive urine flow follows the causative lesion only after a latent period of one to two weeks⁴ If one excludes the transient polyurias observed by Claude Bernard and successors after injury to the floor of the fourth ventricle, on the apparently justifiable grounds that they are due to vasomotor adjustments or to indirect stimulation of the pituitary, the fact remains that permanent polyuria has been produced only by lesions located somewhere along the supraoptico-hypophyseal tract Thus a reasonable explanation is afforded for the fact that extrapituitary lesions can result in a condition remediable by extracts of the posterior lobe itself, and the clinical portent of such disturbances as skull fracture, encephalitis, suprasellar tumor and basilar meningitis is plain

Were this the entire story, however, it is obvious that total hypophysectomy or clinical lesions which destroy the whole gland would likewise result in diabetes insipidus There must be another essential factor, and von Hann²⁴ is given credit for first suggesting that the disease cannot occur unless functioning anterior lobe tissue is present In a considerable number of clinical autopsies, all marked by destruction of the posterior lobe of the pituitary, he pointed out that the only ones with diabetes insipidus were those with viable anterior lobe tissue This astute observation has been supported by those who have consistently produced permanent polyuria in the dog and rat by simple extirpation of the posterior lobe^{16, 21, 22} Although many early investigators reported that polyuria frequently occurred after total hypophysectomy it is generally believed now that these transient increases in urine volume are not comparable to diabetes insipidus^{*} and that uncomplicated excision of the entire hypophysis is not a cause of polyuria²⁵

Thus a state of normal water balance seems to be in part dependent upon a balance between the diuretic property of the anterior and the antidiuretic activity of the posterior lobes That extracts of anterior lobe tissue evoke diuresis has been repeatedly demonstrated,^{26, 27, 28, 29, 30} and Pencharz, Hopper and Ryneerson²² have produced transient oliguria in rats by excision of the anterior lobe alone In this respect as in others, however, the activity of the anterior lobe is complicated by interglandular relations Biasotti²⁸ and White and Heinbecker³⁰ have confirmed the finding of Barnes, Regan and Bueno²⁷ that anterior lobe extracts do not produce diuresis in thyroidectomized dogs Mahoney and Sheehan²⁹ found that the polyuria which followed crushing of the pituitary stalk in dogs was promptly and completely abolished by thyroidectomy and rapidly reestablished by feeding desiccated thyroid, it should be noted, however, that these polyurias were not assuredly permanent and that enormous doses of thyroid were used Fisher and Ingram⁵ then showed that the more permanent polyurias following

* Transient postoperative polyurias may well be due to vasomotor readjustments, to the greater stability of circulating anterior lobe hormone, or to unintentional stimulation of the anterior lobe or pars tuberalis, as evidenced by the experiments of Ingram and Barris³

hypothalamic puncture in cats were greatly diminished though not abolished by thyroidectomy, and White and Heinbecker³⁰ reported that the transient post-hypophysectomy diuresis in dogs was quickly abolished by the same procedure. Heinbecker and White¹⁵ have several times observed that the permanent polyuria caused by hypothalamic injury in dogs is diminished by thyroidectomy to about the same extent as that in Fisher and Ingram's cats.

In two species, then, the diuretic property of the anterior pituitary is modified by thyroid activity, and the rapidity with which urine flow parallels thyroid administration or withdrawal suggests that the mechanism is not wholly explained by variations in the rate of tissue oxidation. It has been claimed that the diuretic and thyrotropic principles of the anterior pituitary are identical.²⁷ Gaebler,³¹ however, observed no correlation between the changes induced in the water metabolism of his almost completely thyro-parathyroidectomized dogs by anterior lobe extracts and the variations in basal metabolic rate. Dix, Rogoff and Barnes³² found that neither anterior lobe extracts nor thyroid substance induced diuresis in depancreatized dogs despite the usual elevations in pulse and basal metabolic rate, and White and Heinbecker³⁰ felt that the diuretic and thyrotropic hormones could not be identical because anterior lobe extract, ineffective in thyroidectomized dogs, produced diuresis when combined with thyroid in doses too small to increase urine flow when the thyroid was given alone. Regardless of the exact identity of this diuretic principle in the anterior pituitary, however, it is of further importance to decide whether changes in water output induced thereby are due to a specific water-regulating substance elaborated in the thyroid or whether they are due simply to the generalized acceleration in tissue metabolism. Even should it be proved that the thyrotropic hormone, working through the thyroid, is responsible for the diuresis the possibility still remains that the thyroid itself exerts an effect on water exchange distinct from that on tissue respiration.

Similar studies not having been reported on man or monkey, it was decided to perform total thyroidectomy on a human subject with diabetes insipidus to determine if possible (1) the effect on urine flow under controlled conditions, (2) whether his sensitivity to pitressin might thereby be increased and (3) whether thyroid and other metabolic stimulants affect water exchange in different manners. We were aware, of course, that species differences might result in a disappointing reduction in urine flow.

There were other but less compelling reasons for believing that ablation of the thyroid might materially lessen urine output. The occasionally striking diuretic efficiency of thyroid substance has long been known. Eppinger³³ described the opposing effects which thyroidectomy and thyroid administration have upon the renal elimination of water and sodium chloride and showed how the rate of absorption of saline from subcutaneous tissue paralleled the rise in metabolic rate induced by thyroid. Dietel and Ditsch³⁴ claimed that pituitrin and thyroxin exert antagonistic changes in the elec-

trolyte distribution of various tissues, and others have shown ³⁶ how thyroxin accelerates the interchange of salts and water between tissues and blood. Most of those who have studied the effect of thyroidectomy upon the pituitary have emphasized the anterior lobe hypertrophy ²⁵ but Herring, ³⁷ who thought that the hyaline material in the posterior lobe might represent pituitrin in visible form, found this material greatly increased after thyroidectomy, although later ³⁸ he reported that removal of the thyroid did not enhance the physiological potency of posterior lobe extracts. A specific effect of posterior lobectomy upon the thyroid apparently has not been found nor has the thyroid in clinical diabetes insipidus been described as visibly abnormal. Pal ³⁹ claimed to get beneficial results in Graves' disease from injections of pituitrin, Gottdenker ⁴⁰ described an antagonism between pituitrin and the thyrotropic hormone, and Peczenik and Popper ⁴¹ reported that pituitrin prevents the thyroid hyperplasia due to anterior lobe hormone. Strauss ⁴² once observed clinical diabetes insipidus disappear with the onset of spontaneous myxedema.

In brief, then, the von Hann-Richter-Ranson theory holds that diabetes insipidus is due to hypopitressinemia in the presence of a diuretic hormone from the anterior pituitary. It is admittedly not a perfect hypothesis but no other has been proposed which harmonizes so many facts and against which there are so few objections. Some of the objections which have been raised are negative ones in the sense that they represent real gaps in our knowledge of pituitary physiology e.g., the pars tuberalis is so closely adherent to the base of the brain as to make complete hypophysectomy to date an impossible achievement. Atwell ⁴³ has attributed certain diuretic effects to extracts of the pars tuberalis but the function of this structure is virtually unknown. Similarly, it has been impossible to extirpate the pars intermedia alone or to remove the posterior lobe cleanly from it but Fisher's tissue assays ⁸ in experimental diabetes insipidus make it appear unlikely that this portion of the gland has anything to do with mammalian water metabolism.

On the positive side there are certain observations which prevent unqualified acceptance of the modern theory. It has been claimed ^{11, 44, 45, 46} that hypothalamic injury will produce diabetes insipidus in a previously hypophysectomized animal, a phenomenon which if true almost certainly eliminates hormonal participation. White and Heinbecker ³⁰ have reviewed the evidence for this statement and conclude that it does not deserve complete support because the protocols lack adequate proof that anterior lobe tissue was absent or because the resulting polyurias were brief and possibly spontaneous. In view of such claims, however, it has been suggested that after hypophysectomy the tuber cinereum and hypothalamus vicariously assume the rôle of pituitrin manufacture ⁴⁷ but the previously mentioned biological assays make this appear improbable, ⁸ and the impossibility of removing all of the tuberal and anterior lobe cells suggests that these post-

hypophysectomy punctures may have served only to stimulate production of diuretic material

Again, if polyuria is due to the unrestrained diuretic effect of the anterior pituitary it is difficult to understand why extracts of this lobe do not induce diuresis in normal rats or increase the polyuria of hypophysectomized rats⁴⁸ and why implants of fresh tissue from the same source do not increase urine flow in hypophysectomized rats²²

Mahoney and Sheehan²³ found that diabetes insipidus could be produced by clipping the pituitary stalk in dogs but not in monkeys, they point out, however, that the monkey differs from the dog in that it is much easier to sever his stalk without hypothalamic injury than it is the dog's, that the nerve tracts in the stalk are more poorly developed, and that differences in blood supply probably account for the fact that stalk occlusion does not induce the same amount of posterior lobe atrophy that it does in dogs

More recently Keller, Noble and Hamilton⁴⁹ reported that in five dogs they severed the stalk at its junction with the hypothalamus without injury to the anterior lobe, the pars intermedia or the hypothalamus and with minimal damage to the pars tuberalis, in several animals a slight increase in water consumption followed but none developed diabetes insipidus. Subsequent cauterization of the "proximal surface" of the separated gland induced marked polyuria, which soon disappeared in four dogs, and remained as a permanent diabetes insipidus in one. They also terminated a chronic hypothalamic polyuria by removal of the pituitary, an experiment reminiscent of Crowe, Cushing and Homans' early finding⁵⁰ that if anterior lobe tissue were immediately transplanted into hypophysectomized dogs polyuria continued until the transplant was removed*. The inconsistent feature of this report is the non-appearance of polyuria after denervation of the posterior lobe. The authors' description seems to indicate that, due perhaps to a more intact blood supply, there was less functional impairment of the separated gland than has usually occurred. This does not invalidate the conception that diabetes insipidus is in part due to hypopitressinemia but may indicate that destruction of the supraoptico-hypophyseal tract does not produce the same degree of posterior lobe insufficiency in the dog that it does in the cat.

Reference should also be made to the paradoxical capacity of certain subjects with diabetes insipidus to retain water⁵¹ and salt⁵². The German school has long maintained that the disease is due to inability of the kidneys to concentrate electrolytes, a defect readily explainable by the hypopitressinemia theory, but it is less understandable why at least some individuals with diabetes insipidus should retain extra salt and water for long periods of time under conditions which should permit maximum excretion³⁴.

Finally, and perhaps most puzzling of all, is the refractoriness of some diabetes insipidus subjects to pituitrin. Biggart's suggestion⁵³ that pituitrin

* In a subsequent paper¹⁶ Cushing said that the same phenomenon accompanied transplantation and removal of posterior lobe tissue. So far as can be determined these conflicting observations have not been reconciled.

is effective only in the presence of intact hypothalamic nuclei apparently no longer holds, but the modern theory also offers no plausible explanation unless one is prepared to believe that diabetes insipidus can exist as the result of a chronic stimulus to diuresis arising in the pituitary

So far as the thyroid is concerned, it is not clear why thyroidectomy abolishes the transient experimental polyurias and only partially inhibits the permanent ones. In any event, it is not thought that the thyroid plays more than a secondary rôle in clinical diabetes insipidus but it is hoped that the observations reported below show that its diuretic effect, limited as it is in humans, is not due solely to its capacity to accelerate cellular metabolism

CASE REPORT

W. D., a 55-year-old male negro, entered Barnes Hospital in the summer of 1936 complaining of polydipsia and polyuria of one year's duration. His previous health had been good, and the physical examination was unimportant except for moderate obesity and hypertension.

Laboratory Data Blood count erythrocytes 5,010,000, hemoglobin 105 per cent, leukocytes 6,400, eosinophiles 5 per cent, basophiles, myelocytes and juveniles 0 per cent, stabs 3 per cent, segmented 55 per cent, lymphocytes 33 per cent, monocytes 4 per cent. The urine was normal but on an unrestricted ward diet each 24 hour output averaged about 10 liters with a usual specific gravity of 1.002. Blood Kahn reaction, 4 plus. Lumbar puncture yielded a clear fluid under normal pressure containing 4-6 lymphocytes per cu. mm., a 2 plus Wassermann reaction, a colloidal gold curve of 2545555500, and protein content of 110 mg. per cent but a negative Pandy. Basal metabolic rate, minus 16 per cent. Plasma cholesterol 292 mg. per cent. Visual fields and roentgen-ray of the pituitary region negative.

Methods The patient was placed on a diet containing less than 2 gm. of sodium chloride daily, extra salt was given him in a weighed shaker and the daily intake calculated by assuming that the diet contained 2 gm. and adding to this whatever salt was not returned in the shaker. It is believed that the recorded figures are accurate to less than 1 gm. daily. He was allowed to eat as much as he wished but the actual daily intake of protein, fat and carbohydrate was carefully weighed.* He usually consumed about 75 gm. of protein and 2000 calories daily.

Total thyroidectomy was performed by Dr. Peter Heinbecker on August 1, 1936.⁵¹ Figure 1 is a section from the removed gland. The extreme resting phase may perhaps be correlated with the basal metabolic rate of minus 16 per cent but it is interesting to note that the pathologist on his initial report remarked that the appearance was not unlike that of thyroids from hypophysectomized animals.

Chart 1 depicts the water and sodium chloride output before and after thyroidectomy, the postoperative figures were obtained after the basal metabolic rate had fallen to an apparently constant low level of minus 35 to 40 per cent and the plasma cholesterol had risen to 490 mg. per cent. Unfortunately urinary nitrogen was not determined until the day of operation. Comparison of periods 1 and 6 when the diet contained an excess of salt shows that the average daily urine output had fallen by about 2 liters, a result similar to the finding of Fisher and Ingram⁵ that thyroidectomy diminished the diuretic effect of sodium chloride in cats with experimental diabetes insipidus. Periods 2 and 7 show an increased response to pitressin after operation although the figures are not strictly comparable because of the greater salt intake during the preoperative interval. In periods 3 and 8, when the salt intake had been re-

*I am heavily indebted to Miss Isabel Grasser for her meticulous supervision of the diets.

duced to 5 gm daily, it is seen that the average urine output in the two periods is practically identical, leading to the conclusion that in this instance thyroidectomy was no more effectively antidiuretic than a low salt diet. Periods 4 and 9 are believed to be comparable and again show that after operation the patient's sensitivity to pitressin was appreciably increased. Stern and Gilligan⁵⁵ had found that individuals with artificial myxedema were no more sensitive to pituitrin than normals. In period 5 desiccated thyroid in doses sufficient to raise the basal metabolic rate from minus 16 per cent to plus 7 per cent did not augment urine flow. Certain of the following observations suggest that the anticipated diuretic response did not occur because the

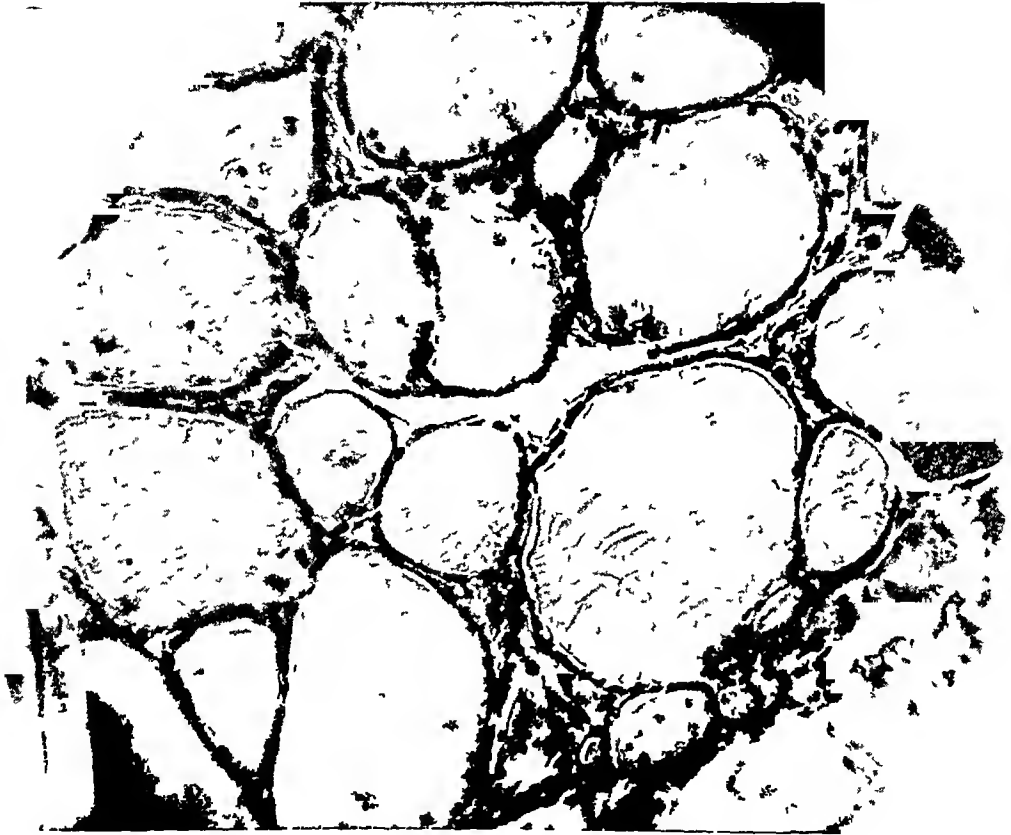


FIG 1 High-power view of ablated thyroid

patient was on a restricted salt intake. The postoperative nitrogen figures indicate increased protein storage.

As stated above, it has not been possible to decide whether the stimulating effect of thyroid upon water excretion is simply one expression of a general increase in metabolic processes or whether it is due to some more specific mechanism. Believing that information bearing on this point might be obtained by raising the postoperative basal metabolic rate to its former level with thyroid and again with some dissimilar agent under conditions which should permit maximum urine flow, the patient was placed on a generous salt intake and first given enough dinitrophenol to elevate the metabolic rate to about the preoperative level. Chart 2 shows the daily urine output and nitrogen balance under these circumstances and under subsequent thyroid administration. Dinitrophenol for five days promptly raised the basal metabolic rate to

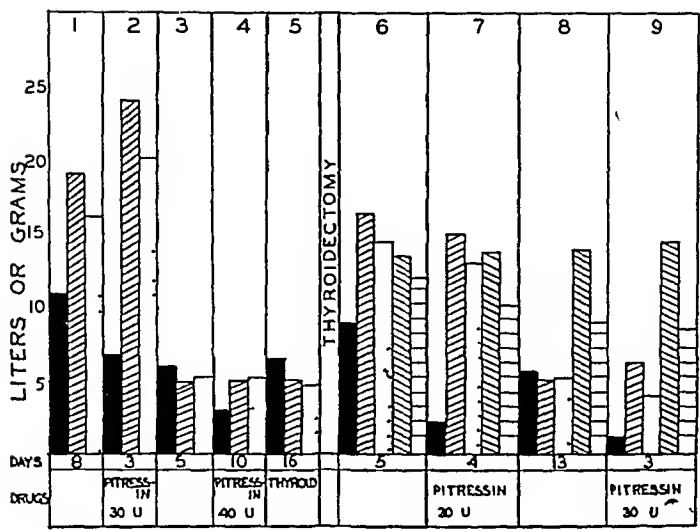


CHART 1 The columns in each period are the averages for the number of days indicated below

■ —24 hour urine output
▨ —sodium chloride intake
□ —sodium chloride output
▩ —nitrogen intake
▧ —nitrogen output

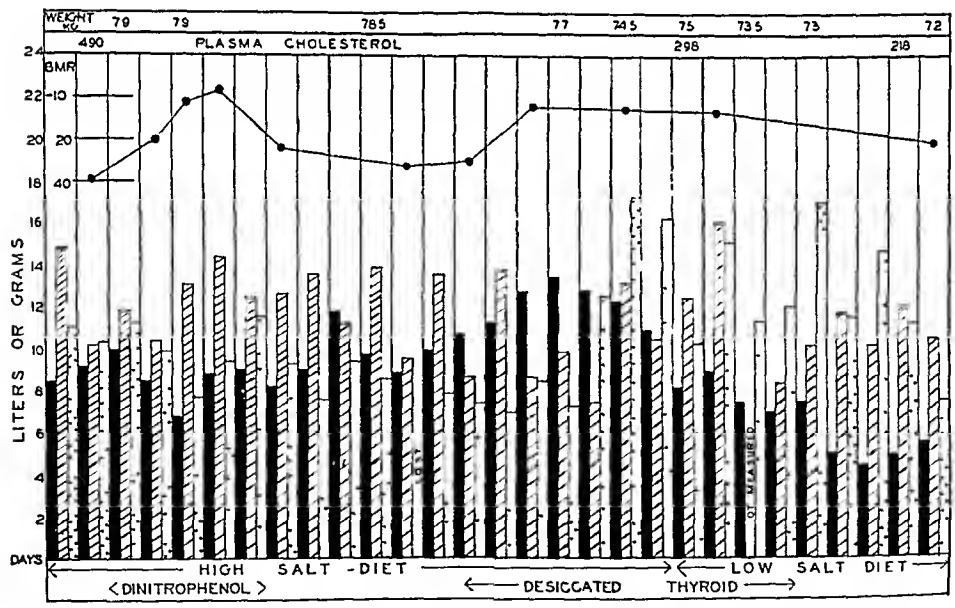


CHART 2 Effect of dinitrophenol and of thyroid upon the excretion of water and nitrogen in diabetes insipidus Each group of 3 columns represents one day

■ —urine output
▨ —nitrogen intake
□ —nitrogen output

minus 10 per cent but no diuresis occurred, the nitrogen balance remained virtually unchanged and there was no appreciable loss of weight. After the metabolic rate had fallen the procedure was repeated with thyroid and, so long as the high salt diet was continued, there was an unmistakable increase in urine volume, withdrawal of extra salt diminished this diuresis despite continuance of thyroid but did not abolish it. The nitrogen balance became strongly negative, plasma cholesterol dropped and the patient lost weight rapidly. These findings confirm the statement⁵⁶ that the rate of protein oxidation is not increased by dinitrophenol and indicate that the diuretic activity of thyroid is not wholly explained by the general increase in tissue metabolism. Heinbecker and White¹⁵ in one dog in which thyroidectomy had diminished a chronic polyuria produced by hypothalamic puncture, also found urine flow increased by thyroid feeding but not by dinitroresol.

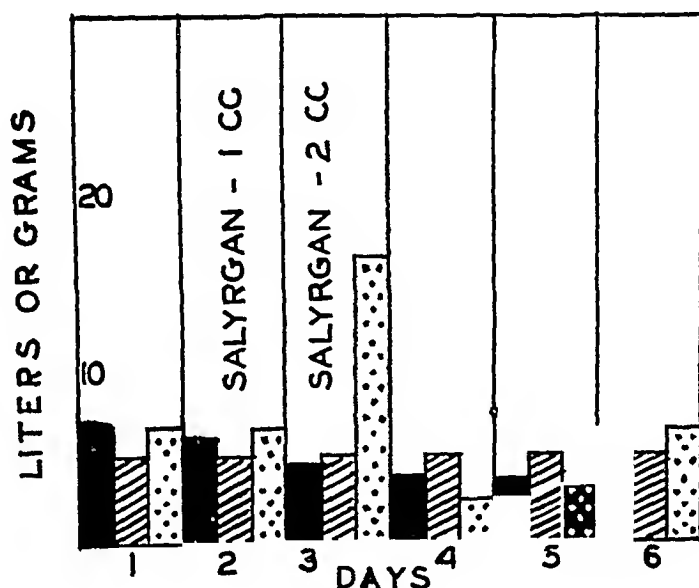


CHART 3 Effect of salyrgan on chloride excretion in diabetes insipidus

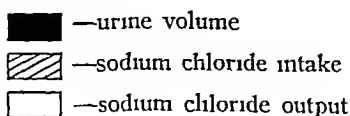


Chart 3 shows that the chloride output may be increased by salyrgan in diabetes insipidus as in normals, a point of some interest in view of the emphasis placed by some⁵² upon the constant hypotonicity of the urine in diabetes insipidus as an etiological factor. This observation was made preoperatively.

It may be incidentally remarked that in the preoperative period also we were unable to effect a greater reduction in urine volume by the combined use of pitressin and 1.8 gm of amidopyrine daily than by pitressin alone. Postoperatively the patient was given 100,000 international units of Progyron-B daily for one week in a theoretical attempt to produce oliguria by inhibition of the anterior pituitary, but without demonstrable result.

By December 1936, four months after thyroidectomy, a definite hypochromic anemia had developed: erythrocytes 4,460,000, hemoglobin 78 per cent, leukocytes 10,200, eosinophiles 3 per cent, basophiles, myelocytes and juveniles 0, stabs 7 per

cent, segmented 53 per cent, lymphocytes 30 per cent, monocytes 7 per cent. The electrocardiogram indicated progressive myocardial damage but the characteristic changes of myxedema had not developed. The patient's general appearance and behavior had not changed and it is only fair to state that he regarded himself as definitely improved by the operation. The non-protein nitrogen of the blood had not departed significantly from its normal preoperative level.

COMMENT

This report is not intended as a rigidly controlled experiment in human physiology. Obviously no guarantee can be made that all thyroid tissue was removed although the drop in basal metabolic rate and the rise in blood cholesterol indicates that the operation was as thoroughly performed as could be expected. It is poor therapeutics to substitute one disease for another and we are not inclined to repeat the procedure. The patient's subjective satisfaction, his increased response to pitressin and his ability to tolerate larger quantities of salt without commensurate polyuria suggest that the operation might be of some benefit to pitressin-resistant individuals in view of the theoretical possibility that this type is due rather to overactivity of the anterior pituitary than to hypopitressinemia.

In the absence of microscopic proof of absent thyroid tissue we cannot, however, claim that thyroidectomy in humans is less effective in reducing the polyuria of diabetes insipidus than it is in the experimental disorder of cats and dogs. That the thyroid exerts an appreciable effect on water exchange has been demonstrated and it is believed that this comes about either through its ability to sensitize the organism to a specific diuretic principle from the anterior pituitary or through a specific diuretic activity of its own.

SUMMARY

1 Current views regarding the etiology of diabetes insipidus are presented and the secondary rôle of thyroid activity assessed.

2 The changes in water, sodium chloride and nitrogen metabolism induced by total thyroidectomy in a human with diabetes insipidus are described. Although ablation of the thyroid was no more effective in reducing urine output than a low salt diet it definitely increased the patient's reactivity to pitressin and diminished his diuretic response to sodium chloride.

3 Comparison of the urine volume response to dinitrophenol and to desiccated thyroid suggests that the diuretic activity of thyroid is not due solely to its ability to elevate the metabolic rate.

4 Under the influence of salyrgan the kidneys of an individual with diabetes insipidus eliminated urine rich in chloride. Therefore, if diabetes insipidus is primarily due to inability of the kidneys to concentrate urine, the defect is not irreversible.

ADDENDUM

Since this was written several pertinent papers have appeared. Keller and Hamilton⁵⁷ oppose the Ranson school in reporting that complete denervation of the

posterior pituitary of cats does not always result in diabetes insipidus, they evidently place more emphasis upon their negative results than upon their successes. Keller⁵⁸ induced chronic polyuria in a dog by hypothalamic puncture, abolished it by hypophysectomy, and then reestablished it first by anterior lobe injections and again by thyroid feeding. He too feels that anterior lobe is necessary for the existence of diabetes insipidus but apparently believes that the diuretic and thyrotropic hormones are identical. McConnell⁵⁹ has reported striking amelioration of diabetes insipidus in a woman by removal of a thyroid adenoma, the fact that her polyuria was said to be uninfluenced by pituitrin in any form intensifies our desire to repeat these observations on pitressin-resistant individuals. Cutler's results from thyroidectomy were apparently not striking.⁶⁰

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SUBACUTE BACTERIAL ENDOCARDITIS ACTIVE CASES WITHOUT BACTEREMIA *

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FOR several years I have been interested in the group of patients with active bacterial endocarditis without bacteremia during life. These cases are not infrequent, and since organisms can be isolated from the vegetations post mortem, it is a matter of some interest to gather more information regarding the nature of the local lesion in the valves and the mechanism concerned with the absence of bacteremia.

The relative incidence of these so-called "bacteria free" [†] cases varies in the experience of different observers. In the last 54 cases of endocarditis which came to necropsy at the Boston City Hospital, [‡] the blood cultures and the heart's blood cultures at postmortem examination were negative in 13 or 24 per cent of the cases. In all of these the organisms were cultured from the vegetations and found by microscopic examination of the heart valves. Other observers report that in anywhere from 15 to 25 per cent of the cases which are observed, bacteremia cannot be shown to be present.

At this time, I present a summary of 15 cases which I have observed during life and at post mortem, including the clinical features, the histologic picture of the valves, and some observations regarding the bactericidal activity of the blood in patients with bacterial endocarditis.

ANALYSIS OF CASES

Of the 15 cases, all showed fever at some time during the course of the disease which lasted from six weeks to 12 months. Ten of the patients were between 21 and 40 years of age, one was under 20, and four were between 41 and 50 years. Seven gave a history of previous attacks of rheumatic fever occurring from one to 36 years before the onset of symptoms suggesting bacterial endocarditis. In two, there were congenital bicuspid aortic valves. All of the patients had heart murmurs. The aortic valve was involved alone in seven instances, and in combination with a mitral valvular defect in three. The mitral valve was involved alone in two cases, and the tricuspid alone in three. All of the individuals had an anemia.

* Read before the St. Louis meeting of the American College of Physicians, April 23, 1937.

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[†] The term "bacteria free" cases was first introduced by Libman.² Sometimes it refers to cases without bacteremia but with organisms in the heart valves. In other instances, the term has been further restricted to those cases in which one can not obtain bacteria from the heart valves at necropsy (healing or healed bacterial endocarditis).

[‡] I am indebted to Dr. Parker, Director of the Mallory Institute of Pathology, for allowing me to use the records for this information. He has also been very generous in studying the sections of the heart valves with me.

Emboli were present in the lungs in all of the cases with right-sided valvular defects. The brain, spleen, kidneys, and extremities were the favorite sites for emboli in the peripheral circulation. A mycotic aneurysm of the superior mesenteric artery was found in one case and small infarcts of the intestine with melena in two. The heart's blood culture was negative at post mortem in all, except two that showed a terminal invasion by bacteria: one a Friedlander bacillus sepsis, the other a hemolytic streptococcus sepsis. In all cases organisms were cultured from the heart valves.

For purposes of discussion it is convenient to divide the cases into groups according to their outstanding clinical features during the course of the disease. I have separated the present cases into those with (1) right-sided heart lesions and multiple pulmonary infarcts, (2) symptoms and signs of progressive renal insufficiency, (3) progressive heart failure, (4) hemiplegia, as the outstanding feature, (5) splenomegaly and anemia. The salient features are presented in table 1.

Cases with Right-Sided Valvular Lesions The only conspicuous features of these cases which were not present in the others were the signs of multiple pulmonary infarcts and jaundice. Embolism in the general circulation was lacking but acute diffuse (non-embolic) nephritis was present in all. It has been pointed out in the past by Blumgart³ and others that right-sided bacterial endocarditis may be associated with multiple pulmonary infarcts without bacteremia, and it has been postulated that one of the reasons for the absence of bacteremia is due to the clearing capacity of the lungs. This is undoubtedly a factor but it can not be the only explanation since a number of patients with bacterial endocarditis and infections confined to the right side of the heart have bacteremia⁴. Of considerable interest in these cases is the presence of non-embolic nephritis, a feature of considerable importance in diagnosis. The splenomegaly that occurs is due to an acute splenic tumor, and the jaundice which usually appears late in the course of the disease is probably due to excessive blood destruction, chronic passive congestion of the liver, and the anoxemia following multiple pulmonary infarctions. The following case is an example.

Case 1 A young man, 34 years of age, entered the hospital complaining of cough and frequent attacks of vomiting. His past and family histories were negative. He had always been well until three months ago, when he noticed shortness of breath and paroxysmal attacks of coughing with some blood-streaked expectoration. There was, in addition, some aching pain in the chest, exaggerated by respiratory effort though it was more or less continuous. There was also dull, aching precordial pain and frequent attacks of sweating at night. Three weeks before admission all of his symptoms became exaggerated and his feet began to swell. It became necessary for him to go to bed, and he had remained there for three weeks before he came to the hospital.

Physical examination showed a thin, undernourished young man. His temperature was 102° F, pulse and respiratory rates were 120 and 40 per minute, respectively. The blood pressure was 150 mm of Hg systolic and 70 mm of Hg diastolic. There was moderate dyspnea but no orthopnea. The positive findings included Signs of

TABLE I
Summary of 15 Cases of Bacterial Endocarditis Without Bacteremia

Case No., Age and Sex	Previous Rheumatic History	Signs of Infection	Signs of Valvular Disease	Embolic Phenomena	Heart Failure	Renal Disease	Blood Findings	Duration of Illness	Necropsy Findings	Miscellaneous Features
Patients with Right Sided Valvular Lesions										
1 29 yrs ♀	None	Chills and fever 101-101° F	Systolic murmur over lower end of sternum	Signs of multiple pulmonary infarcts. Rales and pleural friction rub where.	Slight peripheral edema and hepatomegaly	None B P 12/80 mm Hg	R B C 3 600 000-2 500 000 per cu mm Hgb 57-35% W B C 5 600-13 600 per cu mm	6 weeks	Ulcerative endocarditis. Multiple pulmonary infarcts. <i>Streptococcus viridans</i> from heart valves. No signs of previous valve disease	Jaundice Infection followed an abortion 6 blood cultures during life were negative
2 34 yrs ♂	None	101-103 F	Systolic and diastolic murmur over lower end of sternum	Signs of pulmonary infarction. Cough. Hemoptysis. Cyanosis. None else where.	Enlarged liver. Dyspnea. Slight peripheral edema	Urine showed red blood cells exists albumin B P 113/70 mm. Hg	R B C 2 922 000 per cu mm W B C 32 400 per cu mm. Hgb 42%	3 months	Acute endocarditis, tricuspid valves (<i>Staphylococcus aureus</i>) Septic embolus in pulmonary artery—infarcts left lung—serofibrinous pleurisy. Acute glomerulonephritis. Ascites. Hydropneumothorax.	Jaundice 3 blood cultures during life were negative
3 33 yrs ♂	Pains in joints at age of 14 yrs	99-100 4° F	Systolic murmur at lower end of sternum	Signs of pulmonary infarction in cough. Pain and pleurisy where.	Dyspnea. Dependent edema	Urine showed albumin, red blood cells, casts and leukocytes. Sp Gr 1.016 B P 180/100 mm Hg. Phthalen 20% 2 hrs CO ₂ 28 vol. % N P N 48.8-96.8 mg per 100 cc	R B C 2 636 000 per cu mm Hgb 42%	4 months	Tricuspid endocarditis (<i>Streptococcus viridans</i>) Chronic passive congestion of liver. Pulmonary infarct with emphysema. Chronic glomerulonephritis. Terminal <i>B. Friedländer</i> bacteremia	Blood cultures negative until day before death then <i>B. Friedländer</i> . Parovaginal ureteral fibrillation. Death from renal insufficiency
Patients with Symptoms and Signs of Renal Insufficiency										
4. 48 yrs ♂	None	No fever	Aortic insufficiency	None	Edema of legs. Dyspnea	Urine showed albumin, red blood cells, white blood cells, casts. Sp Gr 1.012 N P N 105 mg per 100 cc B P 120/0 mm Hg	R B C 3 350 000 per cu mm Hgb 52% W B C 16 800 per cu mm	1 year	Vegetative endocarditis congenital tricuspid valve (<i>Streptococcus viridans</i>) Focal embolic nephritis	Beuspical aortic valve. Course characterized by progressive nephritis and heart failure
5 40 yrs ♂	None	98-101° F	Aortic insufficiency	Infarcts in spleen and kidneys	Edema of legs. Dyspnea	Urine showed albumin, red blood cells, casts. Sp Gr 1.016 N P N 30-106 mg per 100 cc B P 150/60 mm Hg	R B C 3 870 000 per cu mm Hgb 60% W B C 11 000 to 15 000 per cu mm	6 months	Vegetative endocarditis aortic valve. Infarcts of spleen and kidneys. Chronic diffuse glomerulonephritis	Clabbed fingers 5 blood cultures negative Splenomegaly
6 45 yrs ♂	None	99-100 5° F	Systolic and diastolic murmur at apex and base	None	Edema of extremities	Urine showed albumin, red blood cells, rare casts. Sp Gr 1.011 1 017 Phthalen 52% 2 hrs B P 165/80 mm Hg N P N 50 mg per 100 cc	R B C 3 440 000 to 2 125 000 per cu mm W B C 10 000 to 13 000 per cu mm	1 year	Vegetative endocarditis, aortic and mitral valves (<i>Streptococcus viridans</i>) Healed infarcts in kidney and spleen. Chronic diffuse nephritis	
7 30 yrs ♂	8 years ago	No fever	Systolic murmur at apex	Infarct of intestine	Generalized edema	Urine showed albumin, red blood cells, casts. Sp Gr 1.011 B P 160/100 mm Hg N P N 80 mg per 100 cc CO ₂ 21 vol %	R B C 2 392 000 per cu mm W B C 15 200 per cu mm Hgb 35%	8 months	Vegetative endocarditis mitral valve and wall of aorta (<i>Streptococcus viridans</i>) Chronic diffuse nephritis. Infarct of jejunum	Splenomegaly Melena Diffuse petechial hemorrhages in skin

Case No. Age and Sex	Previous Rheumatic History	Signs of Infection	Signs of Valvular Disease	Embolie Phenomena	Heart Failure	Renal Disease	Blood Findings	Duration of Illness	Necropsy Findings	Miscellaneous Features
8 2½ yrs ♀	1 year ago	100-101° F	Systolic and diastolic mur at apex	None	None	Urine showed albumin red blood cells casts Sp Gr 1.016-1.020 N P N 50-60 mg per 100 cc Phthalen 9% 2 hrs B P 180/120 mm Hg	R B C 4 300 000 per cu mm Hgb 75% W B C 45 100 to 20 100 per cu mm	6 months	Vegetative endocarditis mitral and aortic insufficiency Diffuse nephritis Bronchopneumonia	
9 3½ yrs ♀	18 years ago	Slight fever for 1 week 100-101° F	Systolic mur at apex	None	Dyspnea Edema	Urine showed albumin red blood cells white blood cells N P N 80-120 mg per 100 cc B P 160/70 mm Hg Sp Gr 1.011-1.013	R B C 1 700 000 to 2 000 000 per cu mm W B C 4 950 to 10 050 per cu mm Hgb 30-35%	4 months	Bacterial endocarditis mitral and aortic valves (<i>Streptococcus viridans</i>) Acute embolic glomerulonephritis	
Patients with Symptoms and Signs of Cardiac Insufficiency										
10 18 yrs ♂	30 years ago	99-100° F	Systolic and diastolic mur at apex	Petechial hemorrhages	Dyspnea Palpitation Edema	Urine showed albumin and casts Sp Gr 1.023 to 1.030 N P N 30 mg per 100 cc B P 140/80 mm Hg	R B C 3 300 000 Hgb 72-52% W B C 3 500 to 8 600 per cu mm	6 months	Vegetative endocarditis on mitral and aortic valves (<i>Streptococcus viridans</i>)	Clubbed fingers 11 blood cultures were negative Edema progressive
11 43 yrs ♂	None	99-102° F	Aortic insufficiency	None	Edema Dyspnea	Urine showed albumin red blood cells white blood cells N P N Phthalen 55% 2 hrs N P N 32-40 mg per 100 cc B P 130/20 mm Hg	R B C 2 730 000 per cu mm Hgb 55% W B C 15 200 per cu mm	11 months	Vegetative endocarditis aortic valve Anasarca Cirrhosis of liver	Bicuspid aortic valve Splenomegaly 25 blood cultures were negative
12 30 yrs ♂	None	95-100° F	Aortic insufficiency	Hemiplegia	Dyspnea Orthopnea Edema	Urine showed albumin and red blood cells Sp Gr 1.020 N P N 33 mg per 100 cc B P 140/20 mm Hg	R B C 3 060 000 per cu mm Hgb 54% W B C 7 300 per cu mm	6 months	Vegetative endocarditis of aortic valve with rupture (<i>Streptococcus viridans</i>)	
Patients with Symptoms and Signs of Cerebral Embolism										
13 37 yrs ♂	None	100-8-102° F	Aortic insufficiency	Hemiplegia Renal infarcts	Dyspnea Edema of extremities	Urine showed Sp Gr 1.024 albumin red blood cells white blood cells and casts N P N 12-80 mg per 100 cc P S P 39% 2 hrs B P 110/50 mm Hg	R B C 4 310 000 per cu mm Hgb 70% W B C 18 000 per cu mm	7 months	Vegetative endocarditis aortic valve (<i>Streptococcus viridans</i>)	12 blood cultures negative Terminal hemolytic streptococcal bacteremia
14 22 yrs ♂	9 years ago	99-103° F	Aortic insufficiency	Hemiplegia Petechial hemorrhages	None	Urine showed albumin red blood cells B P 110/70 mm Hg	R B C 4 100 000 Hgb 84-57% W B C 11 500 to 19 100 per cu mm	0 weeks	Vegetative endocarditis mitral and aortic valves (<i>Staphylococcus aureus</i>) Infarcts in spleen—kidney	Splenomegaly 8 blood cultures negative
Patient with Splenomegaly and Anemia										
15 14 yrs ♀	10 years ago	101-102° F	Mitral and aortic insufficiency	Left lower extremity	Dyspnea Edema	Urine showed albumin red blood cells, white blood cells, and casts N P N 21 mg per 100 cc B P 110/70 mm Hg	R B C 2 100 000 per cu mm Hgb 10-15% W B C 0 800 to 25 100 per cu mm	6 months	Vegetative endocarditis of mitral and aortic wall	Splenomegaly spleen reaching to umbilicus

solidification of the lung over the right lower lobe and a fibrinous pleurisy, moderate distention of the abdomen, an enlarged liver, and edema of the legs. The heart was moderately enlarged and there was a to-and-fro murmur over the precordium with systolic accentuation, which was best heard over the tricuspid area. The murmur was well localized and was not transmitted to the axilla.

Laboratory examination showed a red blood cell count of 2,952,000 per cubic millimeter, hemoglobin of 58 per cent, and a white blood count of 32,400 per cubic millimeter. Blood Wassermann was negative. The urine showed albumin and a moderate number of casts and red blood cells. The blood culture on admission was negative. There was no clubbing of the fingers.

The course of his illness was characterized by irregular fever, varying from 100° to 103° F. The pulse rate varied from 100 to 130, and the respiratory rate from 28 to 36 per minute. The spleen was not palpable. There were no petechial hemorrhages observed and no signs of peripheral embolism to the extremities. Four blood cultures during the course of a month were all negative. He continued to complain of recurrent attacks of pain in the chest, and signs of fluid appeared in both pleural cavities. Cyanosis became a feature of the illness. Finally, four days before death, the skin and sclerae had a definite icteric tint and the urine contained bile pigment. He failed gradually and died one month after admission, the total duration of the illness from the onset of symptoms being four months.

The necropsy showed endocarditis of the tricuspid valves, septic emboli in the pulmonary artery, with infarcts in the lung, sero-fibrinous pleurisy, acute diffuse glomerulonephritis, and a small encapsulated empyema between the lobes of the right lung. There was a moderate hydropericardium and ascites.

In short, then, this was a young man who had the symptoms and signs of an acute infection with fever, tachycardia, increased respiratory rate, signs of myocardial insufficiency, an enlarged liver, edema of the extremities, a systolic murmur over the precordium, a friction rub over the lungs, hematuria, jaundice, repeated negative blood cultures, and a progressive anemia with leukocytosis. The clinical features of the case suggested a right-sided valvular disease with multiple pulmonary infarcts and an acute, diffuse glomerulonephritis.

To sum up, in these cases the symptoms and signs of infection, the signs of right-sided valvular disease (tricuspid or pulmonary insufficiency), multiple pulmonary infarcts without signs of emboli in the greater circulation, with or without the signs of nephritis, and the late appearance of jaundice are the outstanding clinical features. Hemoptysis may be a feature in these patients and results from either pulmonary infarcts or mycotic aneurysms of the pulmonary vessels. These characteristics are highly suggestive of a bacterial infection localized on the right side of the heart.

Cases with Renal Insufficiency One of the most frequent signs of bacterial endocarditis with bacteremia is a focal embolic glomerulonephritis. In most instances, there are indications from the examination of the urine, such as hematuria, which suggest embolic lesions. In a few cases with bacteremia, the renal damage is so great that definite signs of renal insufficiency command attention, and one may find nitrogen retention, acidosis, and moderate hypertension.

In some of the cases with negative blood cultures during life and active lesions in the endocardium from which bacteria can be isolated, progressive renal insufficiency is a conspicuous feature. In the present group, focal embolic lesions were found in eight cases, and in the remaining seven the process was that of a diffuse glomerulonephritis.

In seven cases there were conspicuous signs of renal insufficiency as manifested by albuminuria, hematuria, loss of concentrating power, nitrogen retention, acidosis, and moderate hypertension. The most important features of these cases are the signs of progressive renal failure in an individual with valvular heart disease, with the symptoms and signs of a chronic infection and embolic phenomenon. The following case is an example.

Case 2 A 45 year old man complained of swelling of the face and feet. His family and past histories were negative. He stated that he had always been quite well until one month before admission to the hospital when he began to notice shortness of breath on slight exertion. His shoes became tight, especially at night, and his face and scrotum were swollen. In addition, he noted that his urine was somewhat cloudy and dark red in color. He became increasingly thirsty and passed more urine than formerly. His sleep was disturbed on account of nocturia. He had been in bed for one week before admission to the hospital. He had lost weight and his appetite had become progressively less.

Physical examination showed a well nourished and developed man who was alert and cooperative. His temperature was 101° F, pulse rate 80 per minute, and respirations varied between 20 and 25 per minute. The heart was enlarged to the left, measuring 14 cm. in the sixth interspace and extending 3 cm. to the right of the midsternal line in the fourth interspace. There was a harsh systolic murmur at the apex and base, and a soft blowing diastolic murmur in the aortic area. Lungs were clear. Blood pressure was 165 mm. of Hg systolic and 80 mm. of Hg diastolic. The abdomen was negative and there was slight edema of the ankles.

Laboratory examination showed a red blood count of 3,440,000 per cubic millimeter, hemoglobin of 55 per cent, and a white blood count of 14,800 per cubic millimeter. Specific gravity of the urine varied from 1.011 to 1.017. There was a slight trace of albumin, rare red blood cells and white blood cells, and no casts. Phenolsulphonphthalein excretion was 42 per cent in 2 hours.

After a period of several months in the hospital he improved, as far as his edema and symptoms were concerned, but the albuminuria persisted. The red blood cells had disappeared from the urine. He was discharged and returned six months later, complaining of increasing edema, slight dyspnea, nocturia, and loss of weight.

Physical examination at that time showed that he was dyspneic and cyanotic. He had râles at both lung bases and signs of aortic and mitral regurgitation. The liver was moderately enlarged and there was tenderness over it. There was extensive edema of the legs and scrotum.

Laboratory examination showed that the specific gravity of the urine varied from 1.010 to 1.015. Urine contained large amounts of albumin, many hyaline and granular casts, and a few red blood cells and white blood cells. The red blood cell count was 2,940,000 per cubic millimeter, the white blood cell count was 13,000 with a differential count of 75 per cent polymorphonuclears. Electrocardiographic examination indicated nothing abnormal. Blood pressure was 125 mm. of Hg systolic and 52 mm. of Hg diastolic. Temperature ranged between 99° and 100.5°. Non-protein nitrogen was 50 mg. per 100 c.c., gradually increasing to 65 mg. per 100 c.c. Phenolsulphonphthalein excretion was 5 per cent in two hours. Nitrogen retention, progressive anemia, and death followed 10 months after the onset of symptoms.

Necropsy showed Vegetations on the mitral and aortic valves. Heart's blood culture was negative. Streptococci of the viridans type were cultured from the heart valve. There was acute and chronic glomerulonephritis and a few focal embolic lesions, but the conspicuous feature was diffuse glomerulonephritis without embolization.

In summary, then, this man had the symptoms and signs of cardiac and renal insufficiency, with valvular heart disease, low-grade fever, negative blood cultures, and a progressive nephritis, death occurring with renal insufficiency.

Comment The renal lesions that are encountered in bacterial endocarditis have been studied especially in this country by Baehr and his associates^{5,6}. From Baehr's most recent study a number of important facts emerged. In a series of 91 cases of subacute bacterial endocarditis with bacteremia, the kidneys showed embolic lesions in 84 and were normal in five. In two there was a diffuse glomerulonephritis, in one, it was acute and in the other the process was a chronic one. A terminal azotemia was present in six.

In the 57 patients in the "bacteria free" stage the situation was somewhat different. It is well at this point to say that Baehr defines the "bacteria free" cases as those showing persistently negative blood cultures during life and no bacteria in the vegetations at post mortem when they were examined. In these cases he found evidence of healed focal embolic lesions in 34 and glomerulonephritis in 19, or 33.3 per cent.

In short, then, Baehr points out that patients with bacteremia show focal embolic lesions very often and diffuse glomerulonephritis infrequently. In the "bacteria free" cases diffuse glomerulonephritis is more common and the focal glomerular lesions usually show signs of healing.

It is perhaps well worth noting and emphasizing, then, that diffuse glomerular nephritis appears to be a striking feature in the cases without bacteremia. Rich, Bumstead, and Frobisher⁷ have produced nephritis in animals with hemorrhage into the capsules and tubules by injecting bacteria-free filtrates of broth cultures of organisms derived from bacterial endocarditis. From numerous observations at necropsy and from their experimental work, they expressed the opinion that the circulating bacteria and their products were responsible for the nephritis of bacterial endocarditis rather than focal embolic lesions. To account for the varying frequency of glomerular nephritis in patients with subacute bacterial endocarditis, Rich, Bumstead and Frobisher offer the suggestion that the difference may be accounted for by variations in the strain of infecting organism. Baehr has likewise suggested that the presence of streptococci in the blood can not be the sole cause of the glomerular nephritis inasmuch as it is seen most often in cases without bacteremia. It was suggested that the glomerular nephritis was related to the phenomena concerned in or following the death of the bacteria. In brief, one group of investigators feels that differences in the infecting strain of bacteria are of importance, whereas others postulate differences in the immune mechanism of the disease in various indi-

viduals Whatever the final explanation may be, it is well to consider bacterial infection of the heart valves as a cause of glomerulonephritis, and it is also important to appreciate that it is most common in cases without bacteremia

Cases with Cardiac Insufficiency As a late phenomenon, many patients with active bacterial endocarditis and bacteremia develop all of the symptoms and signs of congestive heart failure In these, the symptoms and signs of infection invariably precede those of heart failure A few of the patients with negative blood cultures came under observation with the symptoms of cardiac insufficiency which dominated the illness from the beginning of symptoms The following case is an example

Case 3 A 48 year old man complained of palpitation and dyspnea of three months' duration He had had an attack of rheumatic fever at the age of 12 years but no symptoms referable to his heart and no pains in his joints until three months before admission At that time he began to notice dyspnea, palpitation, and slight edema of the extremities, especially at night On occasions, he had attacks of paroxysmal dyspnea which would awaken him from sleep and cause him to gasp for breath For one month before admission he had had recurrent chills and fever, followed by sweating, progressive weakness, chronic cough, and some pain in the left upper quadrant radiating to his chest and abdomen His past history was essentially negative except for the attack of rheumatic fever Family history was inconsequential

Physical examination showed a poorly developed and nourished man with dyspnea and the appearance of being acutely ill His temperature was 99.5° F, pulse and respiratory rate were 100 and 22 per minute, respectively Blood pressure was 100 mm of Hg systolic and 48 mm of Hg diastolic Positive findings were Moderate enlargement of the heart to the left, a blowing systolic murmur at the apex, and a systolic and diastolic murmur at the aortic area There were râles at both lung bases The abdomen was moderately distended but no free fluid was detected There was slight edema of the extremities and moderate clubbing of the fingers

Laboratory examination showed that the specific gravity of the urine varied from 1.010 to 1.028 There were rare red blood cells and, on occasions, numerous casts The red blood cell count was 3,300,000 per cubic millimeter, hemoglobin 72 per cent, and the white blood cell count 3,500 to 8,600 per cubic millimeter The differential count was normal Sedimentation rate was increased Electrocardiographic examination showed a P-R interval of 0.16 sec and left ventricular preponderance Fluoroscopic examination of the heart showed a dilated pulmonary artery Blood culture was negative

The patient was observed for a period of three months During that time he had low-grade fever, ranging from 99.5° to 100° F He complained of pains in his joints which were controlled to some extent by the administration of sodium salicylate The edema which was present on admission gradually subsided but he continued to have râles in both lungs and attacks of paroxysmal dyspnea The spleen was not felt at any time On a few occasions a few petechial hemorrhages were observed on the lip, the buccal mucosa, and over the arms and chest The course of the patient's illness was one of progressive failure with the predominating symptoms those of cardiac insufficiency, such as dyspnea, restlessness, and moderate edema of the extremities There was a progressive anemia, the hemoglobin declining to 55 per cent, without any response to iron or liver extract therapy Eleven blood cultures taken over a period of three months of observation were all negative

At necropsy, the heart's blood culture was negative The anatomical diagnoses were Healed rheumatic aortic endocarditis, vegetative endocarditis of the aortic

valves. Culture of these vegetations revealed *Streptococcus viridans*. There was chronic passive congestion of the liver and spleen, a few infarcts in the spleen, and a few focal embolic lesions in the kidney.

In brief, then, a patient who had had rheumatic fever at the age of 12 years, develops the symptoms of cardiac insufficiency six months before death. The clinical course during the last three months of his life was characterized by progressive cardiac insufficiency, the signs of a low-grade infection (slight fever, loss of weight, and a progressive anemia), aortic insufficiency, clubbed fingers, petechial hemorrhages in the skin, and persistently negative blood cultures, death resulting from cardiac insufficiency. The heart at postmortem examination showed vegetative endocarditis of the aortic valves from which *Streptococcus viridans* were isolated. The section of heart valve is shown in figure 1.



FIG 1 Vegetation on aortic valve. The deeply staining material at the periphery of the valve is a mass of bacteria.

There were two cases in which hemiplegia was the first indication of bacterial endocarditis, and a third in which splenomegaly was an outstanding feature. They have been summarized in the table.

DIFFERENTIAL DIAGNOSIS

The conditions which are likely to be confused with infective endocarditis without bacteremia are active and progressive rheumatic infections and the cases of non-bacterial thrombotic endocarditis^{8, 9, 10}. The absence of embolic phenomena, splenomegaly, and nephritis and the presence of electrocardiographic changes and pericarditis favors the diagnosis of rheumatic fever. The history of rheumatic fever and a positive nucleoprotein skin reaction is also of assistance.

The cases of non-bacterial thrombotic endocarditis may give rise to greater difficulty in that they may show clinical features which are common to either rheumatic fever or infective endocarditis, in that they may have pericarditis, polyserositis, nephritis, and skin eruptions of lupus erythematosus, but no electrocardiographic changes. Thrombopenic purpura, hemorihagica and deforming arthritis may be features. All these features, together with the course of the disease, are helpful in the diagnosis.

LESIONS IN THE HEART VALVES

In view of the observation that the blood remained sterile in these cases it was of some interest to study the heart valves and vegetations from which organisms were grown at post mortem and compare the finding with cases showing bacteremia.

Histologic Changes in Heart Valves When the sections from the heart valves showing vegetations were studied with the microscope for purposes of comparing the lesions in the cases without bacteremia with those with bacteremia, it was found that it was impossible to distinguish the cases on this basis. Some of the vegetations showed organization and fibrosis, others from the same valve would exhibit no signs of healing. Morphologically, the organisms appeared to be the same although careful studies for differences in their growth characteristics were not investigated.

The sequence of events in the development and advance of the lesions seems to be somewhat as follows. There is an injury or damage to the endothelium of the valvular surface, which is followed by the formation of platelet and fibrinous thrombi, proliferation of the fibroblasts, and endothelial cells. The infecting vegetations are usually superficial, covering the surface of the valve and consisting of masses of fibrin and platelets. The organisms frequently collect and arrange themselves along the border of the vegetations, and beneath them in some cases one sometimes sees masses of leukocytes. In other vegetations it can be seen that the dense clumps of bacteria at the periphery of the thickened layer of fibroblasts are surrounded by a wall of leukocytes and fibrin.

When the vegetations organize, one finds a gradual transformation of the fibroblastic layer into dense connective tissue. The vegetations themselves are covered with dense fibrin and deeply stained material and it appears as

if the vegetations were being completely surrounded by fibrous tissue, and shut off from the circulating blood

The histologic findings in these cases are in accord with those described by Wright ¹ who could find no difference in the vegetations from cases with and without bacteremia

It does not seem that one can account for the absence of bacteremia in these cases solely on a basis of the difference in the anatomic structure of the vegetations on the heart valves. While it can not be proved at present, there is suggestive evidence from animal experimentation that the cases with negative blood cultures probably have a sufficiently high bactericidal power of the blood to maintain the clearing mechanism at a high level of efficiency. The other possibility is that the organisms are growing so slowly that they can be removed as fast as they enter the circulating blood. That they enter the circulating blood from the vegetations is supported by the fact that patients with negative blood cultures often have emboli in the various organs which contain bacteria

COMMENT

It can not be said that the cases without bacteremia differ essentially from those with bacteremia during life, insofar as their clinical features and course are concerned. The total duration of the illness may be the same in both groups, and there may be no distinguishing marks by which they can be separated during life. There is possibly one exception which is noticeable, and that is the incidence of renal insufficiency in the cases without bacteremia. This question has been discussed above and need not be repeated here. No one will deny, however, that renal failure may be observed in cases with bacteremia even though it seems to be less common than in those without bacteremia during life.

Inasmuch as there is difficulty in distinguishing these two groups of patients on a basis of the clinical features and course of the disease, it will be well to review a number of the salient features and facts regarding the pathogenesis of bacterial endocarditis in man and in the experimental animal. In this way, we seek an explanation for the cases under discussion.

THE PATHOGENESIS OF BACTERIAL ENDOCARDITIS IN MAN

In reviewing the conditions in which subacute bacterial endocarditis is seen in man, certain points stand out. First of all, it is generally conceded that it is most commonly observed in individuals who have damaged valves resulting from a previous attack of rheumatic fever or from congenital valvular defects. It is rare when the preceding rheumatic infection has been an attack of chorea ¹¹. In particular, it seems to be especially common in patients who have chronic valvular heart disease and a regular rhythm, of these, the ones who seem to be most vulnerable are those who are in fairly good health, comparatively free from dyspnea and who fail to give a history

of recurrent attacks of rheumatic fever. Patients with aortic regurgitation alone or in combination with mitral valvular disease seem to develop the disease more often than those with distinct signs of mitral stenosis. It is exceedingly rare in syphilitic aortic insufficiency, in individuals without previous cardiac murmurs, and in patients with hypertension. It is practically unknown in patients with a history of previous attacks of heart failure or established auricular fibrillation and, to my knowledge, it has been reported as following a coronary occlusion in only one case¹²

Of the congenital defects, the commonest predisposing lesion seems to be congenital bicuspid aortic valves, and a patent ductus arteriosus. In table 2 I have summarized the various conditions in which it has been observed.

TABLE II

Conditions in Which Bacterial Endocarditis Has Been Observed in Man

- 1 Rheumatic Heart Disease—acute or chronic
 - a* Aortic regurgitation
 - b* Aortic regurgitation with mitral insufficiency
 - c* Mitral stenosis
 - d* Tricuspid insufficiency
- 2 Congenital Heart Disease
 - a* Bicuspid aortic valves
 - b* Patent ductus arteriosus
 - c* Coarctation of aorta
 - d* Subaortic stenosis
 - e* Patent interventricular septum
 - f* Pulmonary stenosis
- 3 Coronary Occlusion
- 4 Thrombotic Endocarditis (Chronic disease)

In short, it can be said that the patients who are likely to develop bacterial endocarditis are those with rheumatic or congenital valvular defects, in a good state of health, with a normal cardiac rhythm. It is not likely to develop in an individual with hypertension, or a normal heart, or in anyone with auricular fibrillation, or in a patient who has had previous attack of congestive heart failure.

In addition to the above factors there are other considerations in the pathogenesis of subacute bacterial endocarditis which require comment, namely, what are the factors predisposing damaged heart valves to infection by bacteria? what is the portal of entry? and why do the organisms localize?

The first question has been discussed and investigated by a number of observers. There have been two main views, namely, that the heart valves are infected by bacterial emboli focalizing in the valves, and that the organisms invade the valves from the outside. That is to say, it is an infection of the surface of the valve.

The chief argument against intravascular emboli being the sole cause of infection of the heart valves is the fact that it is not possible to demonstrate blood vessels in the heart valves of all individuals. On the other hand, it can be shown that bacterial infection of heart valves is most often superficial and the bacteria occur at the periphery of the thrombi on the valves.

Leary,¹³ Mallory and I¹⁴ have demonstrated bacteria in the very early lesions of bacterial infection of the heart valves and endocardium, and the organisms seem to invade the valves from the surface. How then do microorganisms gain a foothold on an injured valve? It is the opinion of Pappenheimer and Von Glahn¹⁵ that most cases of subacute bacterial endocarditis are due to an infection of rheumatic vegetations by microorganisms, and Grant, Wood and Jones¹⁶ have brought forth convincing evidence that platelet thrombi are exceedingly common on damaged or injured valves, and these thrombi serve as peculiarly favorable areas for the localization of bacteria. They found in studying non-bacterial thrombotic endocarditis that these thrombi occurred on valves which were thickened and on the ones in which infective endocarditis is likely to develop. Moreover, Grant has demonstrated platelet thrombi on heart valves which had been experimentally damaged, showing that injury to a heart valve is followed by the deposition of a platelet thrombus. It is now known that non-bacterial thrombotic endocarditis occurs in a variety of conditions⁸ and, in studying this condition further, I have found that these thrombi may become infected and produce a bacterial endocarditis. Table 3 summarizes the conditions in which I have observed non-infected thrombotic endocarditis and the cases in which such thrombi have become infected by bacteria.

TABLE III
Summary of the Conditions in Which Non-Infected and Infected Thrombotic Endocarditis Are Observed

<i>Non-infected</i>		<i>Infected</i>	
Chronic heart disease	3	Chronic heart disease	2
Leukemia	1	Leukemia	2
Appendix abscess	1	Carcinoma	
Pulmonary tuberculosis	2	Cervix	1
		Lung	2
		Stomach	1
		Hypernephroma	1
		Cirrhosis of liver	1
		Stone in the common bile duct	1

It seems clear that either thrombotic or rheumatic endocarditis may serve as a suitable area for bacteria to localize and gain a foothold, and since these thrombi are relatively free from leukocytes, microorganisms are destroyed with difficulty and are able to survive. Since bacterial endocarditis occurs very often in conditions which favor the development of thrombi on the valve leaflets (damaged valves, acute rheumatic and chronic diseases) it is not far-fetched to believe that these thrombi are an important predisposing factor in the pathogenesis of bacterial endocarditis.

I should not like to leave the impression that it is always necessary to have a previously damaged valve in order for bacteria to gain a foothold on the heart valves and thrive. Indeed, it is well recognized that some microorganisms focalize on previously normal heart valves, and it is highly possible, as suggested by Wadsworth, that acute injury to the heart valves by bacteria serves as an excellent predisposing factor for the localization of

infection It is well worth recalling, however, that the majority of cases of *Streptococcus viridans* endocarditis occur in patients with previously damaged valves, and this must be taken into account in any discussion of the pathogenesis of the disease

The question now arises regarding the circumstances that permit bacteremia and the portal of entry for the infecting organism? It is well recognized that it is often impossible to tell when the original invasion of bacteria took place, since the disease begins in most instances in an insidious manner and is not preceded by any previous noticeable infection that would serve as a focus of entry Upon reflection, this does not seem at all curious since it would be surprising if green producing streptococci did not invade the circulating blood frequently since they are present in the mouth from a period shortly after birth and persist until death That they invade the circulating blood in a variety of diseases has been amply demonstrated by Lichtman and Gross,¹⁷ Epstein and Kugel,¹⁸ and Swift and Kinsella,¹⁹ and one knows that they often invade the blood following tonsillectomy and the extraction of teeth There are now on record a number of cases of subacute bacterial endocarditis in which the disease first asserted itself following the extraction of teeth or tonsillectomy, or respiratory infections, and one is also familiar with the cases that follow local areas of suppuration²⁰

In addition to the presence of thrombi on the heart valves and the bacteremia, it is necessary to account for the localization of bacteria It is a general rule in bacterial infections that the localization of bacteria in tissues is consistent only in the cases in which there are antibodies present It has been demonstrated by Kinsella,²¹ Wright,²² Miller and Branch,²³ Libman,²⁴ and Swift²⁵ that the blood from patients with active infections and bacteremia shows agglutinins for the homologous organism and is actively bactericidal Spink and I²⁶ have demonstrated that the blood from bacteremic cases is not only capable of killing the organisms which are present in the circulating blood but is often capable of killing many thousands of microbes which are added to it Furthermore, and this we consider of significance, the blood of some normal individuals is highly bactericidal for most strains of *Streptococcus viridans* which have been isolated from cases of proved bacterial endocarditis

To sum up the information regarding the pathogenesis of subacute bacterial endocarditis in man it would appear that a damaged heart valve, the presence of platelet thrombi, transient bacteremia, and the presence of anti-bacterial antibodies which aid in the clearing of the blood stream and the localization of bacteria are all important in determining the development of bacterial endocarditis

EXPERIMENTAL BACTERIAL ENDOCARDITIS

Bacterial endocarditis has been produced experimentally in animals (rabbits,²⁷ dogs,²⁸ horses,²⁹ and chickens³⁰) by several methods and by different

investigators. These observations are of great importance in understanding some of the features of the infection in man.

The observations of Herrmann²³ in regard to endocarditis in dogs are significant. He found that the normal heart valves of dogs were relatively immune to infection by *Streptococcus viridans* when large doses of organisms were injected intravenously. When, however, the aortic valves were injured, a large number of puppies died from the results of a spontaneous streptococcus endocarditis. This was also noticeable in parturient bitches. In all, 20 per cent of his dogs with experimental aortic regurgitation developed spontaneous streptococcus endocarditis. Of further interest, however, it was found that dogs with damaged heart valves were found to be uniformly susceptible to bacterial implantations of streptococci when they were injected intravenously. Similar observations have been made in dogs by Kinsella²⁴. In addition, he found that it was easier to produce endocarditis in dogs when they had been partially immunized. Of considerable interest in respect to the development of endocarditis on the damaged heart valves of dogs are the observations of Grant¹⁶ that platelet thrombi form on the heart valves shortly after they have been ruptured, and it is possible that they serve as foci for the localization of bacteria.

The same kind of experiments have been carried out in rabbits with somewhat similar results, with the exception of the fact that repeated injections of organisms into rabbits with normal heart valves are followed by endocarditis in a certain number of cases. Wright²² has shown that infection of the valves is more likely to occur in animals that have been treated with vaccines so that demonstrable antibodies are present in the circulating blood. It can be shown, however, that when the valves of a rabbit are damaged their resistance to infection is greatly lowered.

The observations of Wadsworth²⁵ on the occurrence of endocarditis in horses are of the highest significance to our understanding of the pathogenesis of bacterial endocarditis. He found that endocarditis developed very frequently in horses that had been immunized against pneumococci. The infection of the heart valves usually took place after the animal had a high antibody titer in the circulating blood and there was no convincing evidence that the infection took place early in the course of the injections. The blood cultures of these animals remained sterile and the organisms in the vegetations were few and could be cultured from the valves with difficulty, and were found in sections of the heart valves in only small numbers at post mortem.

In short, the findings in the horses studied by Wadsworth are similar in many respects to the "bacteria free" cases in man. That is to say, the endocarditis is active, the blood remains sterile. It is perhaps important to recall that endocarditis was produced in these animals without mechanical injury to the heart valves and it did not develop until there was a high antibody titer in the blood—a condition favoring the localization of bacteria.

To sum up this discussion, it may be said that infection of the heart valves is seen most often in animals following mechanical injury and the injection of microorganisms intravenously. Following mechanical injury to heart valves, platelet thrombi form and serve as a focus for the localization of bacteria, and while infection may occur spontaneously, it is most frequent following the injection of bacteria. Furthermore, when there is no previous injury to the valves, endocarditis develops more frequently following repeated injections of organisms into animals which develop active bactericidal antibodies. It would appear, then, that injury to the heart valves, the presence of antibodies, and bacteremia are all important and necessary in the pathogenesis of bacterial endocarditis. It is not at all unlikely in many instances, as suggested by Wadsworth, that the original injury to the valves is bacterial in origin since Leary and Mallory and I have demonstrated bacteria in very early lesions on the heart valves and endocardium.

IMMUNOLOGIC STUDIES IN BACTERIAL ENDOCARDITIS

The immune reactions that can be demonstrated in the circulating blood of patients with bacterial endocarditis have been studied by Kinsella,²¹ Wright,²² Miller and Branch,²³ Swift,²⁵ Libman,²⁴ and ourselves. Inasmuch as these studies have a direct bearing on the problem of the pathogenesis of bacterial endocarditis they are presented in detail. While Kinsella was unable to show that there was any constant identity between the various strains of streptococci isolated from cases of bacterial endocarditis, he demonstrated quite conclusively that the patient's blood serum contained agglutinins and complement fixing antibodies for homologous strains of organisms. Miller and Branch demonstrated homologous agglutinins in their case and Wright²² found that the blood of septicemic cases contained antibodies and was actively bactericidal. Moreover, in animals with bacterial endocarditis there was evidence of antibody production even in the face of an increasing septicemia. Wright considered the bacteremia in bacterial endocarditis to be a secondary phenomenon resulting from an escape of organisms from the lesions in the heart valves and thought that the bacteria increased in the blood stream of his animals because they multiplied in the lesion and were discharged faster than they could be removed. That this is true in man seems to be proved from the remarkable case of subacute *Streptococcus viridans* septicemia which was cured by excision of an arteriovenous aneurysm of the external iliac artery and vein, reported by Hamman and Rienhoff.³¹ In this case, the removal of the focus (vegetations in the aneurysm) was followed by a clearing of the blood stream and complete recovery. This case seems to prove beyond any doubt that the bacteremia in these cases is an overflow phenomenon. In common with Wright, I have found that the cases which are negative are always negative, and since numerous blood cultures were taken during life in all of the cases

reported herewith, it is unreasonable to suppose that faulty technic was responsible for our failure to isolate the organisms during life.

Within recent years it has been found by Howells and Corrigan,³² Levine,³³ Derrick and Fulton,³⁴ and Swift²⁵ that patients with subacute bacterial endocarditis fail to show skin reactions to filtrates of streptococci and we have confirmed these findings in 10 instances. This examination may be of significance in the diagnosis of obscure cases of bacterial endocarditis.

While it has not been proved in the human cases that the reason for the negative blood cultures during life is the presence of a high antibody titer

TABLE IV

Whole Blood Killing Power of Patients with Bacterial Endocarditis and Bacteremia
Maximum number of organisms killed by 0.5 c.c. whole blood Homologous organisms

	10 ⁻¹	10 ⁻²	10 ⁻³	10 ⁻⁴	10 ⁻⁵	10 ⁻⁶	10 ⁻⁷	10 ⁻⁷
Patient 1	0	0	0	0	0	0	0	5
Normal control	0	0	0	0	0	0	0	
Patient 2	0	0	0	0	0	0	0	2
Normal control	0	0	0	0	0	0	0	
Patient 3	0	0	0	0	0	0	0	2
Normal control	0	0	0	0	0	0	0	
Patient 4	0	0	0	0	0	0	0	29
Normal control	0	0	0	0	0	0	0	
Patient 4	0	0	0	0	0	0	0	29
Normal control	0	0	0	0	0	0	0	
Patient 5	+	+	0	0	0	0	0	5
Normal control	+	0	0	0	0	0	0	
Patient 6	+	+	+	0	0	0	0	6
Normal control	+	+	+	+	0	0	0	
Patient 7	+	+	+	0	0	0	0	11
Normal control	+	0	0	0	0	0	0	
Patient 8	+	0	0	0	0	0	0	12
Normal control	+	0	0	0	0	0	0	"
Patient 8	+	0	0	0	0	0	0	"
Normal control	+	0	0	0	0	0	0	"
Patient 8	+	+	0	0	0	0	0	"
Normal control	+	0	0	0	0	0	0	"
Patient 8	+	+	+	+	0	0	0	"
Normal control	0	0	0	0	0	0	0	"
Patient 8	+	+	+	+	0	0	0	"
Normal control	0	0	0	0	0	0	0	"
Patient 9	+	+	+	0	0	0	0	"
Normal control	+	+	+	+	0	0	0	"
Patient 10	+	+	+	+	0	0	0	"
Normal control	+	+	+	+	0	0	0	"

of the blood there is suggestive evidence, from studies on animals and in particular from the studies by Wadsworth, that such is the case. An additional factor is the small numbers of organisms present in the vegetations.

Baehr suggests that some patients with bacterial endocarditis develop an immunity to the infecting organism which is of sufficient degree to kill off the bacteria shortly after the onset of the disease. In this way, he explains the bacteria-free cases. From numerous observations on man and animals it does not seem unreasonable to suppose that the reason for the negative blood cultures is due to the fact that the organisms are removed from the circulating blood as rapidly as they enter it. That they are present in the blood from time to time is attested by the presence of embolic phenomena in these cases. The reason they continue to live in the vegetations of the heart valves is probably due to the fact that the bacteria are situated in an area where there are relatively few leukocytes or tissue phagocytes and the bactericidal action can not operate effectively.

Studies on the bactericidal power of the whole blood of patients with bacterial endocarditis and bacteremia indicate that normal individuals are often able to kill large numbers of organisms that can be isolated from the blood of patients with endocarditis. Likewise, the patients with bacterial endocarditis can do the same. This is illustrated in table 4 and chart 1.

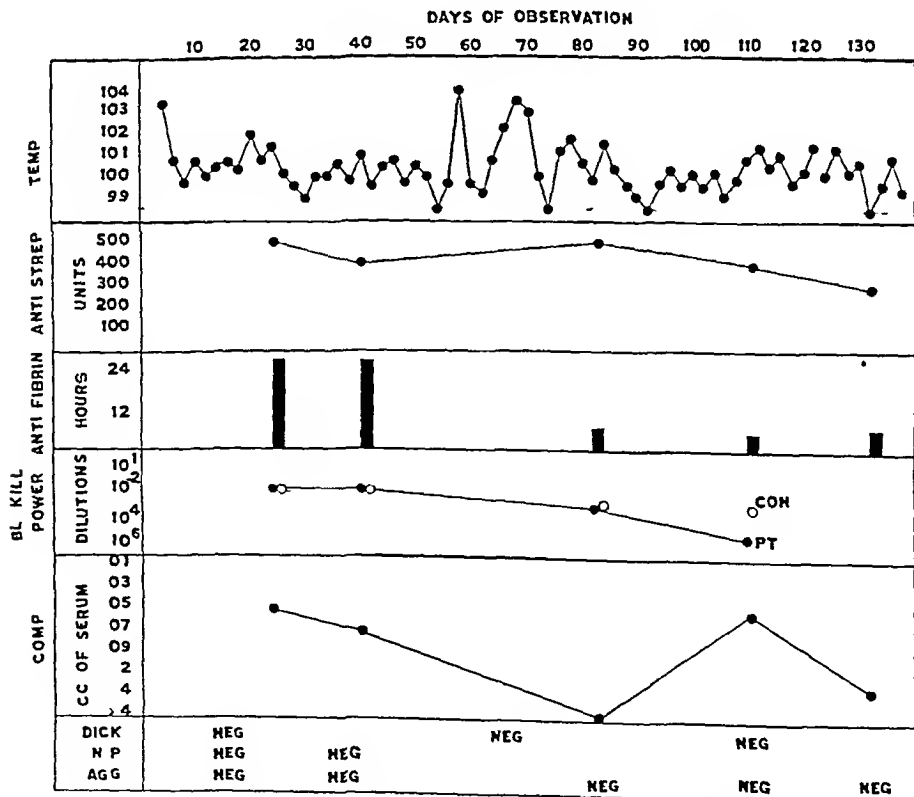


CHART 1 The temperature chart together with the various immune reactions that were followed in a patient with bacterial endocarditis

In short, then, it would appear that normal individuals as well as patients with bacterial endocarditis possess antibacterial antibodies against some strains of *Streptococcus viridans* derived from endocarditis. This is suggestive evidence of a defense mechanism for the clearing of the blood stream of bacteria, once they gain entrance to the circulation. While it is not known whether all of the patients who have immune bodies in their circulating blood at the time of an active infection have had antibodies before the onset of infection, it is suggested by our observations on some normal individuals, that this is possible, although Swift²⁵ records a case in which agglutinins against the homologous organism were not present before infection and appeared after its development. This is a question requiring further study.

SUMMARY AND CONCLUSIONS

A group of 15 cases of active bacterial endocarditis without bacteremia is described and summarized. For purposes of discussion they were divided into five groups: (1) those with right-sided valvular disease, multiple pulmonary infarcts, and jaundice, (2) patients with renal insufficiency, (3) patients with heart failure, (4) patients with splenomegaly and anemia, and (5) patients with hemiplegia.

All of the patients had physical signs of valvular disease. Non-syphilitic aortic regurgitation was present in ten. The mitral valve was involved alone in two and the tricuspid alone in three.

There was no essential difference in the clinical course of the patients with bacteremia and in those without bacteremia with the possible exception of the fact that the non-bacteremic cases were more apt to have renal insufficiency as an outstanding feature of their illness.

The pathogenesis of bacterial endocarditis as it is observed in man and the experimental animal was reviewed and it was pointed out that the following factors are significant: a previously damaged valve, the presence of platelet thrombi on the valves, a transient bacteremia and the presence of antibodies that encourage the localization of bacteria.

Bactericidal studies in the blood of patients with bacterial endocarditis were presented, and it was concluded that some normal individuals as well as patients with bacterial endocarditis have antibodies which are capable of killing organisms derived from cases of bacterial endocarditis.

From the foregoing discussion it seems reasonably plain that bacterial endocarditis can be produced in animals under the same circumstances as exist in man, namely, the presence of damaged valves, platelet thrombi on the valves, bacteremia, and the presence of antibodies. There also is highly suggestive evidence that the human cases with negative blood cultures have a condition analogous to the experimental endocarditis of horses as described by Wadsworth. This, however, requires further study and proof. In any event, it is well to recognize this group of cases since they aid in understanding the infection and should encourage one to look for ways of destroying organisms in the valves.

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DISTURBANCES OF RATE AND RHYTHM IN ACUTE CORONARY ARTERY THROMBOSIS

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INTRODUCTION

INVESTIGATORS¹⁻⁵ during the nineteenth century observed that ligation of the coronary arteries in animals very frequently produced cardiac arrhythmias either transient or severe enough to cause cardiac standstill, but their exact nature was not defined until the beginning of the present century. In 1909, Lewis⁶ reported that after ligation of the left coronary artery multiple premature beats were recorded by venous pulse and electrocardiographic tracings. These frequently formed paroxysms of ventricular tachycardia from which ventricular fibrillation sometimes developed. Subsequent workers⁷⁻¹² confirmed these observations. Recently, in addition, de Waart et al,¹¹ after tying off the right coronary artery found sinoauricular and auriculoventricular block. In all these observations it is noteworthy that auricular fibrillation and flutter were rarely encountered, and auricular and nodal tachycardia only occasionally.⁹

In man also, the majority of authors¹³⁻²¹ have noted the presence of arrhythmias in coronary artery thrombosis. While White²⁰ thinks they occur in only a small number of cases, Levine²² observed them in more than one-fourth of his series. The incidence of the significant arrhythmias, that is, those other than premature beats, in several large series²²⁻³¹ varies between 9 and 27 per cent, the average in over 800 cases being 17 per cent. As in animals, the most common irregularity is premature beats, usually ventricular, which occurred in about one-quarter of the cases. Next in order of frequency is auricular fibrillation. In the reports mentioned above its incidence was usually 6 to 7 per cent, although Levine's²² figures were as high as 23 per cent and Meakins and Eakin's²⁶ 14.5 per cent. Brill,³² too, observed that it frequently appeared early in coronary thrombosis.

The other arrhythmias auricular flutter, auricular and nodal tachycardia, ventricular tachycardia, nodal rhythm and heart block, in the experience of all authors²³⁻³¹ occurred in only a small percentage of cases. Auricular flutter was observed by Parkinson and Bedford²⁴ and Jervell²⁹ in 3 to 4 per cent of cases and by Howard²⁷ in only 0.6 per cent. However, of nine fatal cases of coronary artery thrombosis described by Longcope,³³ four had auricular flutter. Other authors^{28, 34, 35} also observed this ar-

* Presented at the St. Louis meeting of the American College of Physicians, April 22, 1937.

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This study was aided by a grant from Mrs. Charles Altschul, Mr. Frank Altschul and Mr. Herbert H. Lehman.

rhythmia in coronary artery thrombosis. Similarly, auricular and nodal tachycardia occurred infrequently^{24, 28, 36, 37}. Sinoauricular block,^{29, 38} sinus bradycardia^{39, 40} and nodal rhythm^{38, 40, 41, 42} have been encountered but once or twice in any one series. The average incidence of heart block, partial and complete, is 2 to 5 per cent,²²⁻³¹ although Appelbaum and Nicolson³⁷ found three instances in 30 cases. Salcedo-Salgar and White,⁴³ in a recent study of heart block in more than 300 cases of coronary thrombosis, found the incidence to be 4.2 per cent, this figure included 10 cases of partial and only four of complete block. In marked contrast is the experience of Schwartz⁴⁴ who over a period of a few years observed 15 cases of complete heart block with Stokes-Adams syndrome precipitated by coronary thrombosis. In this connection may be mentioned the recent analysis by Graybiel and White⁴⁵ of 72 cases of complete heart block of which approximately 10 per cent followed an acute coronary thrombosis.

Because of the frequency of ventricular tachycardia in experimental coronary ligation⁶⁻¹² its importance in coronary artery thrombosis has been emphasized in numerous case reports in the literature^{8, 22, 42, 46-59}. It is significant, however, that most of the authors have reported one or only a few cases of coronary artery thrombosis with ventricular tachycardia, or rarely, a small series of ventricular tachycardia in which the chief etiological factor was recent or old myocardial infarction⁶⁰⁻⁶³. Analysis of large series of cases of coronary artery thrombosis, however, gives a truer perspective of the rarity of this arrhythmia. Although Levine⁶³ intimates that it occurs in approximately 5 per cent of cases, in 470 cases in the series mentioned above,²³⁻³¹ there were but three cases, an incidence of 0.6 per cent.

It has been found that not infrequently two or more arrhythmias occur simultaneously or in close association^{35, 38, 41, 42, 53, 57, 64, 65}. Hamman¹³ considered such a sequence diagnostic of coronary artery thrombosis.

MATERIAL

An analysis of the arrhythmias found in 300 cases of coronary artery thrombosis is presented in this report (table 1). Excluding premature beats, present in one-quarter of the cases, the incidence of arrhythmias was 14 per cent. Forty-two patients presented the following 46 irregularities:

Auricular fibrillation	22	
Auricular flutter	3	
Paroxysmal tachycardia	9	
auricular		3
nodal		2
ventricular		1
undetermined		3
Nodal rhythm	3	
Wandering pacemaker	1	
Heart block	8	
incomplete heart block with dropped beats		3
complete A-V dissociation		3
combination of both types		2

Prolongation of the P-R interval, which was very common, and bundle-branch block are not included in this paper as they will form the material of a future article. For the same reason A-V heart block will not be considered in great detail.

Significant differences were observed between patients with arrhythmias and those with regular rhythm (table 1). In the former group, the ratio of men to women was 23:1, in the latter 4:1, apparently women are more prone to develop irregularities than men. This applied particularly to auricular fibrillation and heart block. The average age was slightly higher in those with arrhythmias. Furthermore, hypertension and cardiac enlargement occurred in four-fifths of the cases with an arrhythmia, whereas in those without, hypertension was present in 65 per cent and cardiac enlargement in only 60 per cent. Heart failure also was more common when an arrhythmia existed, that is, in 85 per cent as compared to 70 per cent. It is obvious, then, that arrhythmias occurred in the more severely ill patients, a fact further supported by the high mortality rate in this group, 39 per cent as against only 22 per cent in the remainder of the series. The mortality rate for the entire series of 300 cases was 26 per cent. Most of the deaths were in the group with auricular fibrillation and complete heart block. That the arrhythmia may have been merely one expression of the severity of the attack and not the cause of death, however, is probable in view of the fact that half the patients died some time after the cessation of the arrhythmia.

Almost half the arrhythmias appeared during the first three days succeeding the attack and the majority during the first week. In some cases it followed immediately the onset of the attack. However, the arrhythmia may set in at any time, even in the third week. The duration of the arrhythmia was usually short. In over half the cases it lasted 24 hours or less, and in some only a few hours. Auricular fibrillation and paroxysmal tachycardias were as a rule, transitory, heart block and nodal rhythm usually persisted longer, occasionally several weeks.

It is interesting that the presence of previous occlusions did not increase the incidence of arrhythmias. This would indicate that the latter depend upon the acute changes in the heart.

PREMATURE BEATS

Premature beats occurring in 77 patients or one-quarter of the series was by far the most common irregularity encountered. They were ventricular in type in 46 cases, auricular and ventricular in 15, auricular alone in 14 and nodal in two. Multiple premature beats were found very frequently and in nine patients there was bigeminal or trigeminal rhythm (figures 7 and 9). The mortality rate in this group did not differ from the average for the entire series although it should be noted that when auricular or both auricular and ventricular premature beats occurred, the mortality rate was higher (35 to 40 per cent). But this finding might not hold true

TABLE I
Analysis of the Arrhythmias in 300 Cases of Coronary Artery Thrombosis

	Total Control Series	Arrhythmias Excluding Premature Beats	Premature Beats	Auricular Fibrillation	Auricular Flutter	Nodal Rhythm	Paroxysmal Tachycardia	Complete Heart Block	Partial Heart Block
No of cases	300	46	77	22	3	4	9	5	3
Incidence		14.5%	25.7%	7.3%	1.0%	13.0%	3.0%	1.7%	1.0%
Average age	56	58	56	60	61	53	54	61	57
Ratio—male female	39 1	23 1	6 1	21 1	3 0	4 0	8 1	1 4	1 2
Previous attack	47 7%	47.8%	59.7%	50.0%	100%	0	33.3%	80.0%	33.3%
Previous hypertension	64 6%	80.4%	75.3%	86.3%	66.6%	50.0%	88.8%	100%	33.3%
Enlarged heart	60 3%	78.2%	72.7%	81.8%	100%	25.0%	88.8%	80.0%	66.6%
Heart failure	71 0%	84.8%	74.0%	81.8%	100%	25.0%	100%	100%	100%
Mortality	25 7%	38.0%	28.5%	45.4%	66.6%	0	22.2%	80.0%	0
During arrhythmia		19.0%		22.7%	33.3%		0	60.0%	
Later in attack		19.0%		22.7%	33.3%		22.2%	20.0%	
Onset—1-3 days	20	20	20	7		3	3	5	2
4-7 days	11	11	16	8	1	1	1		1
2nd week	11	11	14	5	2		4		
3rd week	4	4	17	2			1		
Duration—1 day or less	25	25	4	12	2	1	8		1
2-3 days	5	5	30*	3					
1-2 weeks	11	11	15	5	1	3	1	1	1
2-3 weeks	1	1	5						
1-2 months	2	2	6	1				1	
Permanent				1					1
Average vent rate				120-150	85-150	60-70	120-180	20-75	50-100

* Two to seven days' duration

in a larger series. Also the fact that the incidence of heart failure was practically the same as in the whole series is evidence that the clinical significance of premature beats is not important.

It has often been stated^{12, 66, 103} that the appearance of frequent ventricular premature beats may be the forerunner of ventricular tachycardia. Yet, this occurred only once in our series, when a fleeting paroxysm of ventricular tachycardia was observed during the course of a bigeminal rhythm (figure 9).

AURICULAR FIBRILLATION

Auricular fibrillation was found 22 times and occurred more frequently in women than in men. The average age of these patients was somewhat higher than in the general series. The incidence of increased arterial tension, enlarged heart and heart failure was definitely greater than in the control group and the mortality rate was high, 45 per cent. The latter was in large degree dependent on the heart failure since half the deaths occurred after the arrhythmia had spontaneously remitted. The average ventricular rate was 120–150 beats per minute (figures 1 and 2) which was undoubtedly associated with the high incidence of heart failure. Several cases, however, had a slow ventricular rate even without the use of digitalis.

The onset of auricular fibrillation usually occurred during the first few days and in two-thirds of the cases during the first week. It is significant that in 12, or more than half of the patients, its duration was 24 hours or less. In one instance it lasted two months and then ceased spontaneously, and in another it became permanent after digitalization. In five patients the irregularity was intermittent, alternating with periods of sinus rhythm.

With a view to the possibility that this arrhythmia might be ascribed to a lesion in a specific area of the heart, electrocardiograms were grouped into types associated with infarction of the anterior (Q_1T_1) or posterior (Q_3T_3) surface of the left ventricle. It was found that with auricular fibrillation, the infarction was as frequent on the anterior as on the posterior surface of the heart. In five of these cases examined at necropsy the right and left coronary arteries were equally occluded.

Digitalis was administered to two patients after the onset of the auricular fibrillation because of severe heart failure. One of these died suddenly on the eighteenth day (figure 3) and the other developed permanent fibrillation although the heart failure was controlled. Two other patients received digitalis before the onset of the fibrillation but it is not possible to state whether the appearance of the arrhythmia was related to the drug.

AURICULAR FLUTTER

There were three patients with auricular flutter, two of whom died (figures 3 and 4). Heart failure and enlarged hearts were found in each instance and all had had one or more previous attacks of coronary throm-

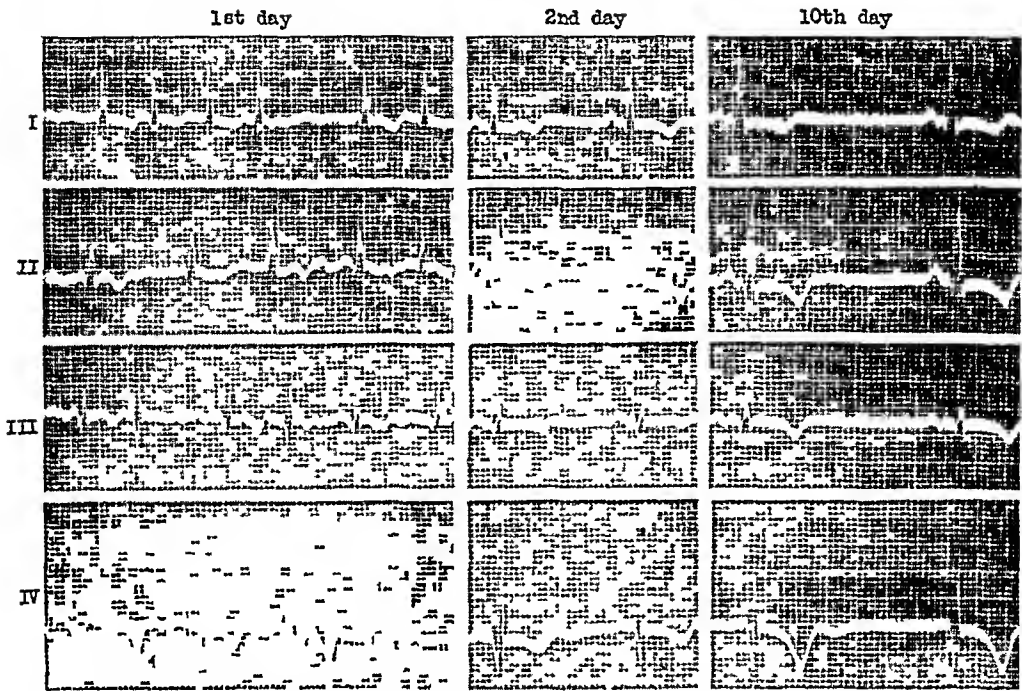


FIG 1 D S, male, aged 61 Acute and old coronary artery thrombosis Recovery
Paroxysmal auricular fibrillation and sinus bradycardia

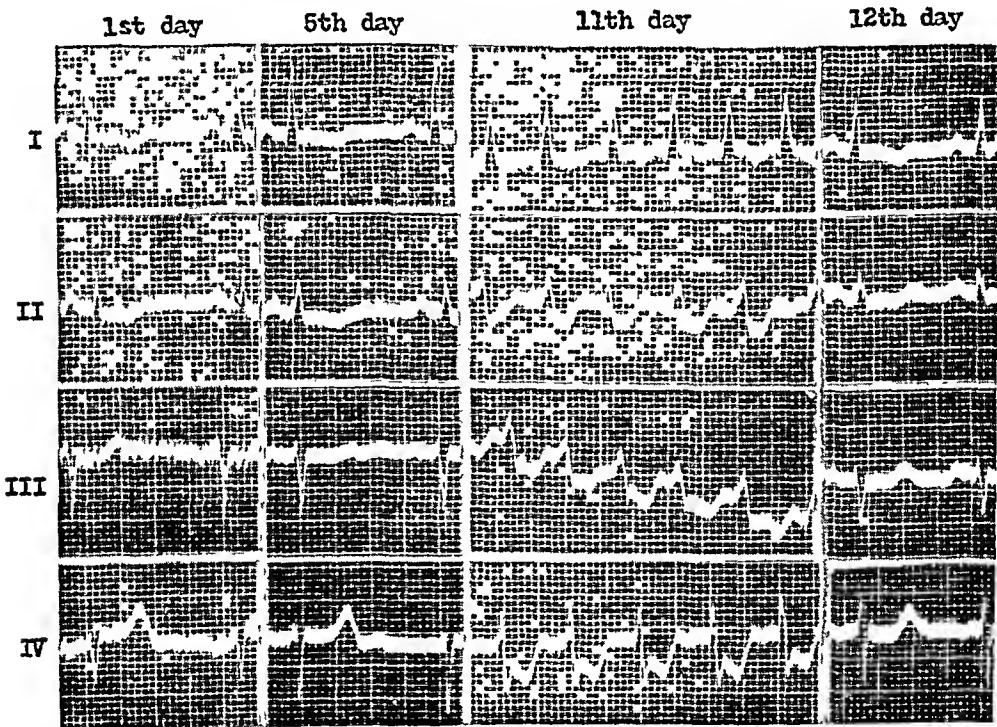


FIG 2 Auricular fibrillation Acute coronary thrombosis in 56 year old male (J K)
Died twenty-fourth day P M Thrombosis of LAD, left and right circumflex coronary
arteries

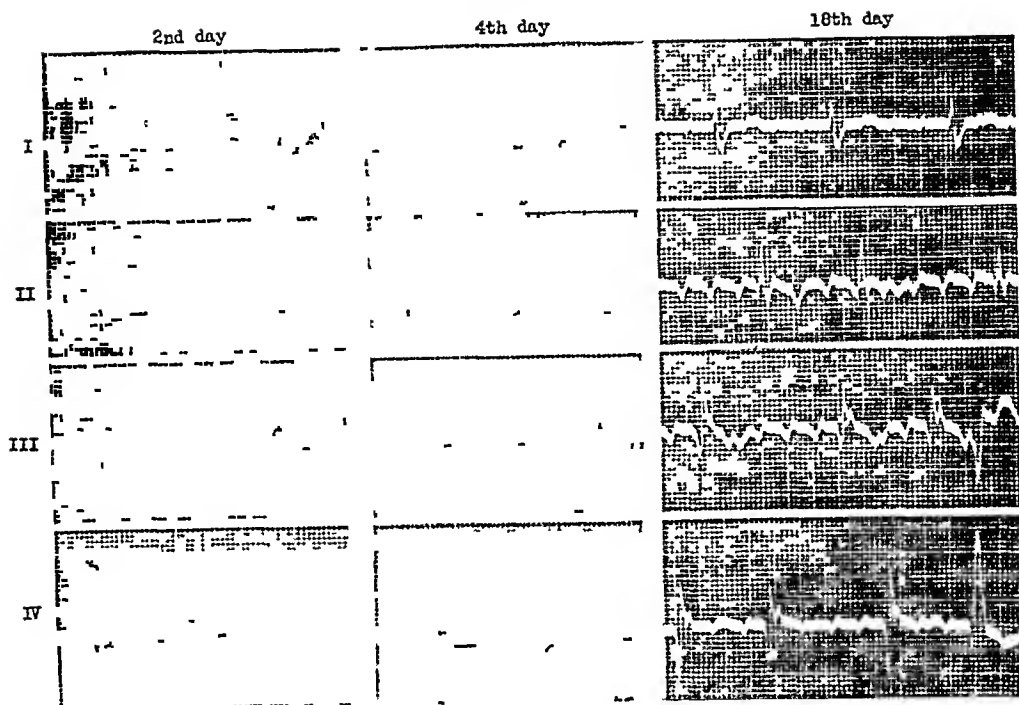


FIG 3 S L, male, aged 67 Old and acute coronary artery thrombosis Paroxysmal auricular fibrillation and flutter Sudden death on the eighteenth day P M Acute right, old LAD and right coronary thrombosis Posterior infarction

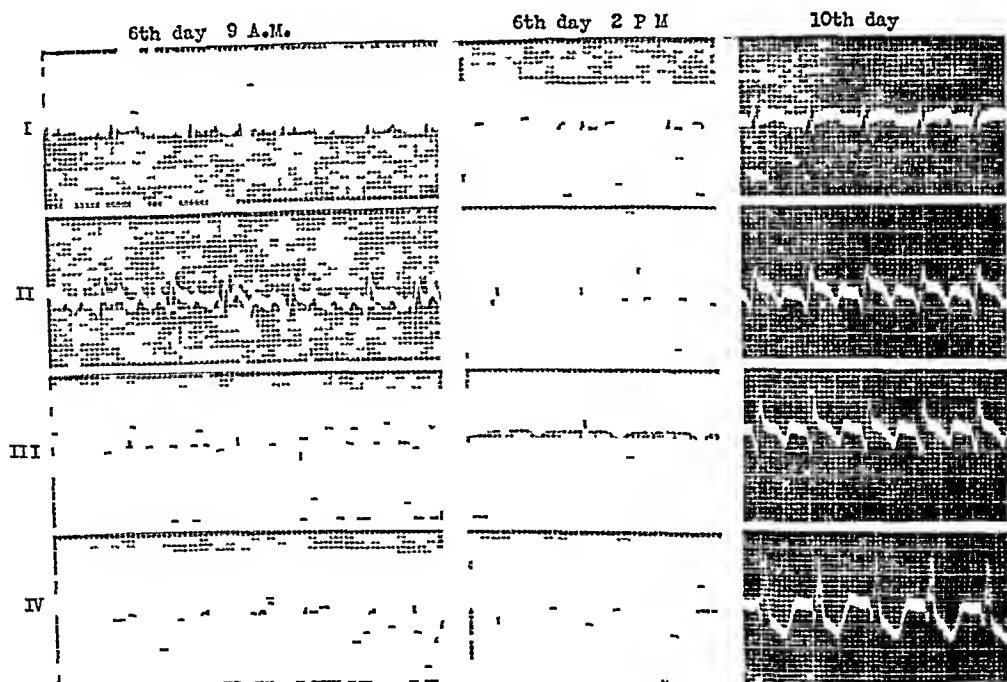


FIG 4 S C, male, aged 58 Old and acute coronary artery thrombosis Paroxysmal auricular flutter Sudden death on thirteenth day

bosis In one of the fatal cases the auricular flutter was a transient episode during auricular fibrillation (figure 3). The two fatal cases had both received digitalis, one during the arrhythmia and one before it set in.

NODAL RHYTHM

There were three cases with nodal rhythm and one with wandering pacemaker (figures 5A and 6). All four patients survived, probably because the ventricular rate was normal, between 60 and 70 beats per minute. The arrhythmias disappeared without treatment within a week. Not all cases of nodal rhythm and shifting pacemaker are due to right coronary artery occlusion as one might expect, for two patients had electrocardiographic signs of anterior wall infarction. Thus the S-A node may be compromised by occlusion of the left coronary artery, either by involvement of its nutrient blood vessel or nerve supply.

PAROXYSMAL TACHYCARDIA

Paroxysmal tachycardia occurred in nine patients. The average ventricular rate was 150 beats per minute. Although all nine patients had heart failure and eight an enlarged heart and hypertension, the duration of the arrhythmia was 24 hours or less in eight of the nine, and only two died. Of the nine cases, three were auricular (figures 5B and 7), two nodal (figure 8) and one ventricular (figure 9). Although the focus of origin was undetermined in three because electrocardiograms were not obtained during the arrhythmia, the clinical appearance was that of an auricular tachycardia.

A word should be added concerning ventricular tachycardia. With constant supervision and frequent electrocardiograms it was observed only once in the 300 cases examined*. Its duration was extremely brief, a few hours, and it remitted without treatment. This observation emphasizes the rarity of ventricular tachycardia in man.

Only two patients with paroxysmal tachycardia received treatment. One with auricular tachycardia who recovered received one dose of 6 grs. of quinidine sulphate. The arrhythmia ended 10 hours later but probably was not influenced by the drug. Another patient with nodal tachycardia was given 54 grs. of quinidine but died of a cerebral embolus four days after cessation of the tachycardia.

HEART BLOCK

Although increased P-R intervals occurred very often, incomplete heart block with dropped beats or complete A-V dissociation was found but eight times in the 300 cases. Three patients had complete heart block alone with

* Since these data were collected, two other cases of ventricular tachycardia have been observed. In one, a 42 year old woman, the arrhythmia persisted despite quinidine therapy by mouth and intravenously and the patient died after two days. Septal infarction without recent thrombosis was found at post mortem. In the second case, a male aged 38, the tachycardia lasted about one day and ceased spontaneously. The patient recovered.

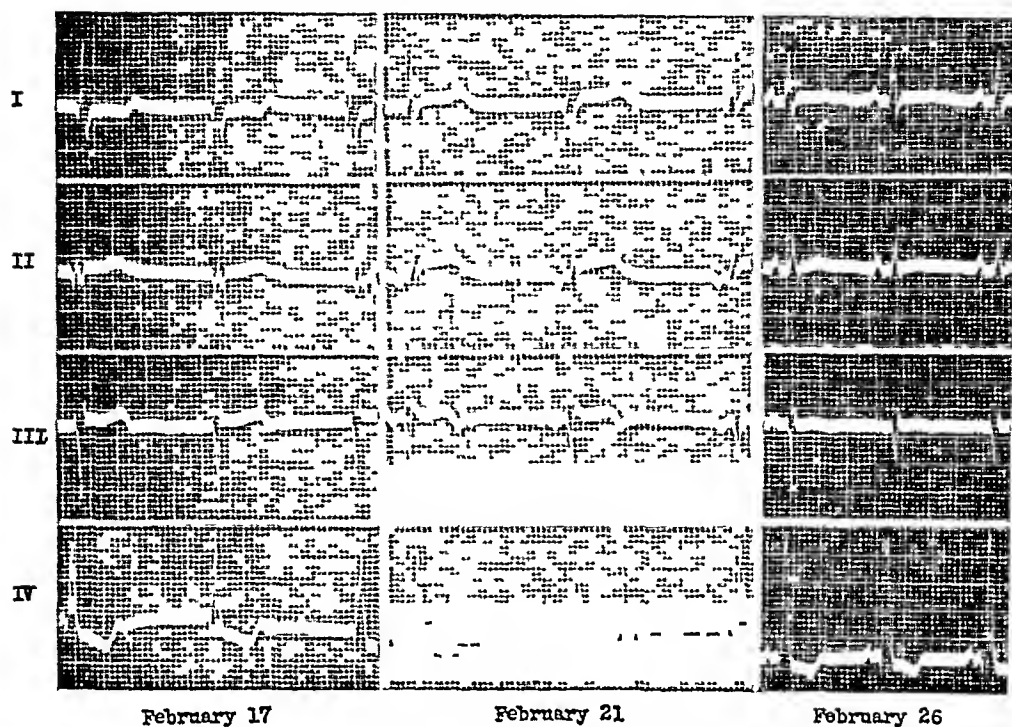


FIG 5A S H, aged 62 Acute coronary occlusion Nodal bradycardia

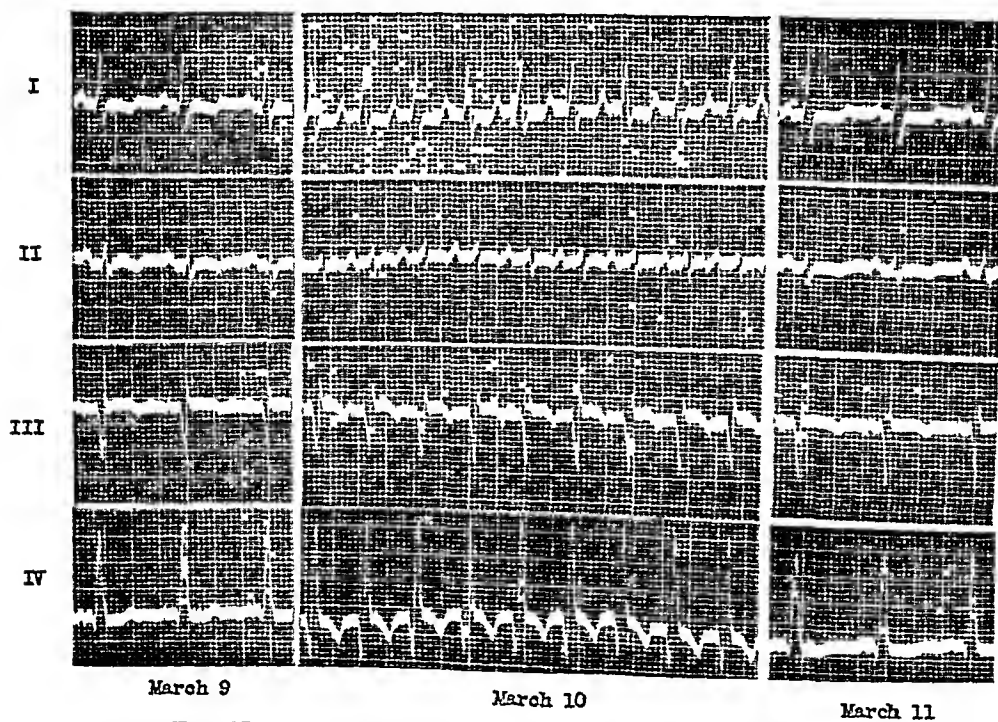


FIG 5B Same patient. Paroxysmal auricular fibrillation

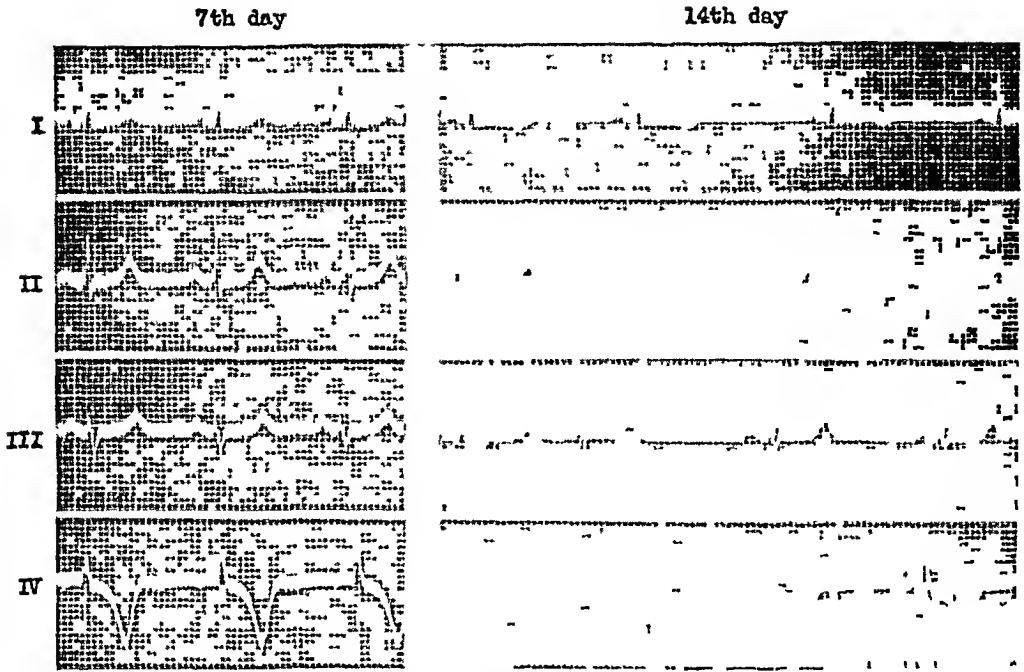


FIG 6 C Z, male, aged 48 Coronary thrombosis Shifting pacemaker
Duration one week

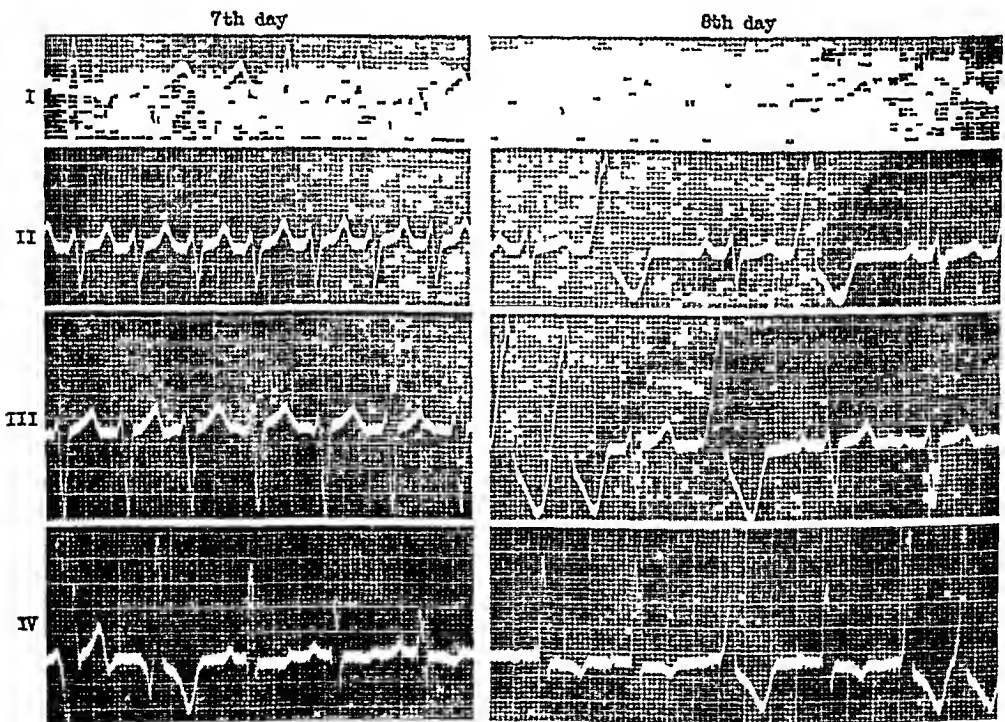


FIG 7 C L, male, aged 48 Coronary thrombosis Auricular tachycardia, ventricular bigemini
Recovered

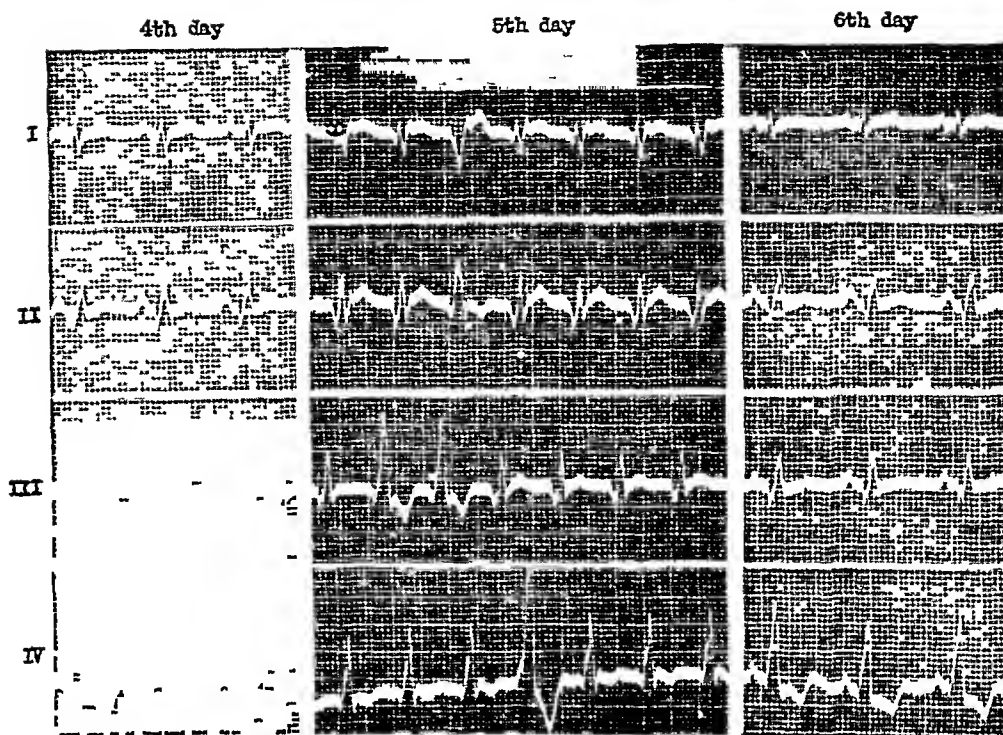


FIG 8 L D, male, aged 61 Coronary thrombosis Nodal tachycardia Recovery

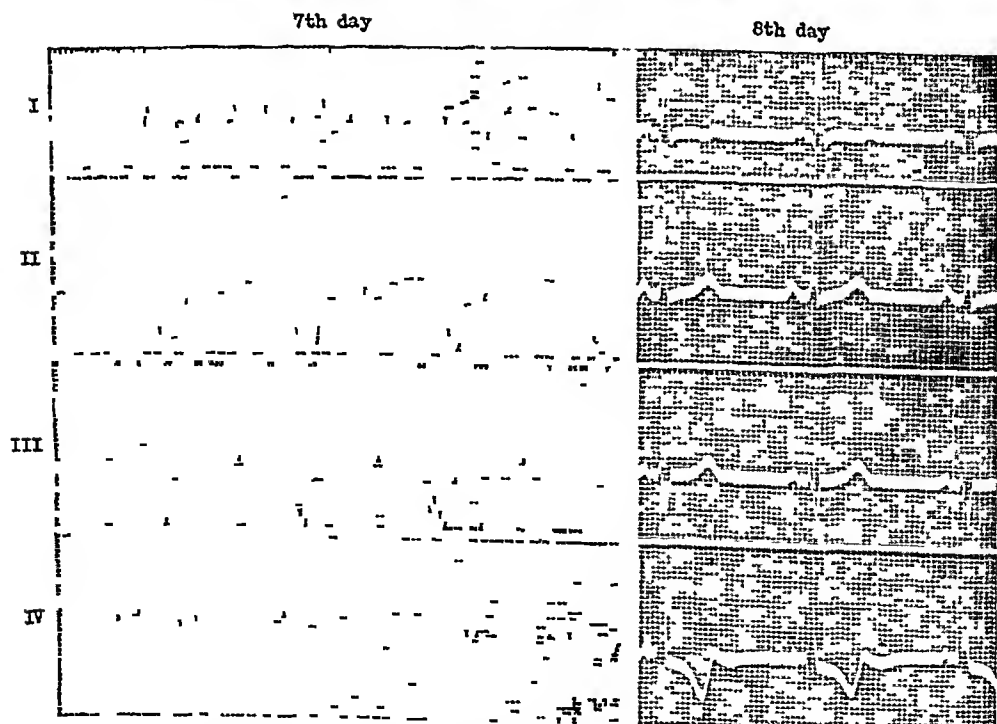


FIG 9 E M, male, aged 56 Coronary thrombosis Recovered Ventricular tachycardia and bigemini

ventricular rates between 20 and 40 beats per minute (figure 10) They all had hypertension, an enlarged heart and heart failure These patients all died within three days after the onset of the arrhythmia In two other patients the arrhythmia varied between incomplete and complete heart block, one of these died of heart failure soon after the rhythm had returned to normal Finally, there were three patients who had incomplete heart block alone The ventricular rate in these cases was higher, 50 to 100 beats per minute, and all three survived In one, the incomplete heart block was still

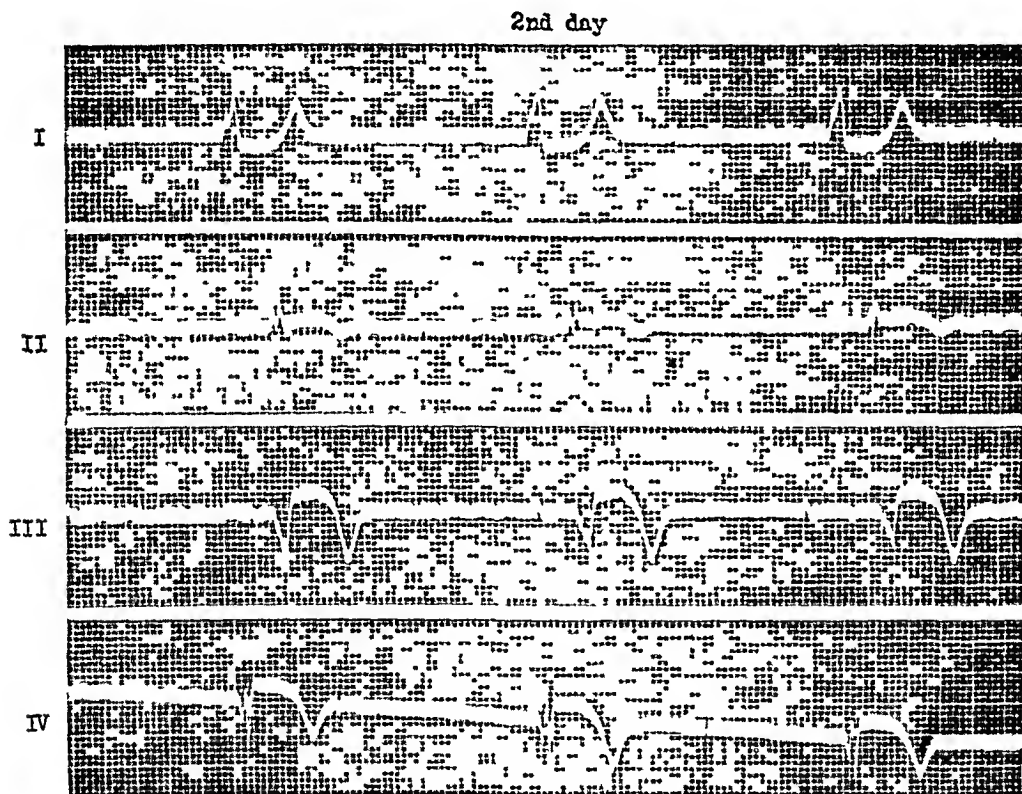


FIG 10 C B, female, aged 72 Coronary thrombosis Complete heart block and auricular fibrillation Death on fourth day P M Right coronary thrombosis Infarction posterior left ventricle and septum

present one year after the attack In the other two, normal sinus rhythm returned gradually within one week

Four of the five patients with complete heart block came to postmortem examination and in each instance there was occlusion of the right coronary artery with infarction of the posterior wall and septum, with or without occlusion of the other arteries, findings which confirmed those of previous investigators^{22, 38, 44, 67, 68} who had noted the association between complete heart block and this specific pathological lesion

One patient with complete heart block received adrenalin before admission to the hospital but with no effect One patient who showed both com-

plete and incomplete heart block at different times received atropine and ephedrine sulphate, again with no effect. The three patients who had incomplete heart block received no treatment and survived.

The heart rate in this group of cases deserves emphasis. The three patients with complete heart block who died were semi-comatose with rates between 20 and 40 beats per minute when admitted to the hospital. We believe that in these cases the outcome depended on the ventricular rate, when it is below 40, the prognosis is poor.

ASSOCIATION OF ARRHYTHMIAS

In three cases two or more significant arrhythmias (figures 3 and 5) were associated and in 10 cases a significant arrhythmia was associated with multiple premature beats as, for example, a ventricular bigemini interrupted by paroxysms of auricular tachycardia (figures 7 and 9). One patient developed nodal rhythm during the first week of his illness, auricular fibrillation during the second week and auricular tachycardia during the third week (figures 5A and 5B).

NORMAL HEART RATE

In 134 patients (44.6 per cent) the heart rate throughout their illness was between 61 and 100 beats per minute (table 2). Enlarged hearts and heart failure were found in only one-half of these, an incidence less than the average of our series. The majority of patients were in their first attack of thrombosis. The mortality rate was only 6 per cent. Therefore, a patient whose heart rate does not go above 100 beats per minute has a very good outlook.

TABLE II
Heart Rate in 300 Cases of Coronary Thrombosis

	Normal Heart Rate	Sinus Tachycardia	Sinus Bradycardia
No. of cases	134	158	70
Incidence	44.6%	52.6%	23.3%
Average age	55	57	54
Ratio—male:female	4:1	3.6:1	10.7:1
Previous attack	44.0%	50.0%	38.6%
Previous hypertension	61.9%	65.8%	60.0%
Enlarged heart	48.5%	69.6%	42.8%
Heart failure	53.9%	84.2%	47.1%
Mortality	6.0%	39.9%	2.8%
Average ventricular rate	61-99	100-150	46-60

SINUS TACHYCARDIA

We have emphasized in a previous study⁶⁹ the importance of tachycardia both as a prognostic sign in coronary thrombosis and as an index of the

degree of heart failure. When the cardiac rate rose above 100, the incidence of cardiac enlargement and heart failure as well as the mortality rate rose, 40 per cent of these cases ending fatally (table 2). The significance of heart rate is particularly evident in those with a rate of 120 or more, heart failure was almost universal and the mortality rate 54 per cent as against 29 per cent in the group with a rate 100 and 120. As previously stated, in patients with a rate between 60 and 100, the mortality rate was only 6 per cent.

SIMPLE BRADYCARDIA

A study of the clinical course of those patients whose heart rate at any time during the attack of coronary thrombosis fell to 60 or below, excluding cases of heart block, is of interest (table 2). These patients did extraordinarily well, and heart failure and mortality rate were minimal. In fact, none of the eight patients whose rate was between 40 and 50 and only two of the 62 whose rate was between 50 and 60 died. The average age of these patients was slightly lower than the average for the series, the majority had sustained their first attack and the incidence of enlarged hearts and heart failure was low.

SYMPTOMS

The onset of an arrhythmia in patients with coronary thrombosis may be of considerable diagnostic significance. Occasionally, it is the first, perhaps the only, sign of the presence of thrombosis, corroborated by electrocardiogram. Therefore, even in the absence of pain, the sudden appearance of an arrhythmia may warrant a tentative diagnosis of coronary artery thrombosis.^{13, 22, 25} The arrhythmia may occasion no symptoms other than palpitation. However, when the ventricular rate is very rapid, the coronary circulation of a heart already severely damaged may become so embarrassed as to cause precordial pain and shock which simulate another acute coronary artery thrombosis.⁷⁰⁻⁷³ In our series, two patients who were recovering from the effects of an occlusion suddenly suffered a recurrence of severe precordial pain and shock. Electrocardiograms during this episode showed in one case (figure 2) auricular fibrillation with a ventricular rate of 150-200 and in the other (figure 5B), auricular tachycardia with a ventricular rate of 170, in addition there were definite R-T deviations characteristic of acute infarction. However, the diagnosis of another acute thrombosis had to be given up when within 24 hours the condition of the patient and the electrocardiogram spontaneously resumed their former status after regular sinus rhythm and a slow rate had returned.

The effect of a very slow ventricular rate, as in complete heart block, may also manifest itself clinically by syncope, convulsions and coma, that is, the Stokes-Adams syndrome. In our experience and that of most authors, the latter is rare in coronary artery thrombosis. However, Schwartz⁴⁴

recently described 15 such cases, although it is possible that not all had coronary thrombosis as the diagnosis could be confirmed by electrocardiogram or necropsy in only a few cases. One of our patients with heart block entered and died in coma, and two others in semi-coma, in the former, an associated cerebral vascular lesion could not be ruled out. Another point not to be overlooked, as Levine²² has emphasized, is that syncope in coronary thrombosis may result from insufficient cerebral circulation as a result of severe collapse. Such an occurrence was observed in one patient of our series.

Levine²² was the first to point out the rarity of coronary artery thrombosis in patients with auricular fibrillation, he observed only one such case and in this the diagnosis was uncertain. Parkinson and Campbell⁷⁴ in 200 cases of paroxysmal auricular fibrillation found 12 associated with coronary thrombosis but in only two was the arrhythmia present before the acute attack. Brown⁷⁵ studied the incidence of coronary thrombosis in patients with auricular fibrillation and coronary sclerosis and found only two instances in 119 cases. In a similar study of 158 hypertensive patients with fibrillation Flaxman⁷⁶ found only three instances of coronary artery thrombosis. In our own series auricular fibrillation may have been present preceding the attack in two patients. The explanation for this antagonism between auricular fibrillation and coronary thrombosis is not clear to us.

THE MECHANISM OF PRODUCTION OF ARRHYTHMIAS IN CORONARY ARTERY THROMBOSIS

When one considers the multiplicity of effects of coronary artery closure on the heart, it is not surprising that arrhythmias are often a complication. In the present state of our knowledge it is, of course, not possible to explain each arrhythmia with certainty. However, certain factors, such as *anoxemia*, *impaired nutrition* or *altered metabolism* of the heart muscle, *increased irritability*, *nervous reflexes*, *anatomical lesions* and *heart failure* are important in initiating any arrhythmia and all these are present to a striking degree in coronary artery thrombosis.

It is impossible to separate anoxemia and impaired nutrition or metabolism of the heart muscle. The effect of coronary thrombosis is not confined to the local area of infarction but disturbs the function of the heart as a whole. During the acute stage of shock there is a marked diminution of cardiac output and mean blood pressure and not only is there a local block in the coronary circulation at the site of the thrombosis, but the blood flow to the rest of the myocardium is reduced. The nutrition of the heart suffers, its metabolic activities are interfered with, and as Neuhof⁶⁴ early pointed out, such disturbances in the auricular musculature produce differences in refractory periods and delays in conduction which may throw the auricles into fibrillation. Carter and his coworkers⁷⁷ emphasized the relation between anoxemia and cardiac irregularities, particularly in coronary throm-

basis. Anoxemia leads to the local accumulation of lactic acid which interferes with the development of the excitatory process and its normal propagation. Thus there may be a local area in which diminished conductivity or spontaneous excitation gives rise to an ectopic rhythm. In particular, anoxemia may decrease the refractory period in the auricles leading to the circus movement of auricular fibrillation and flutter. Carter refers also to the earlier observations of Greene and Gilbert⁷⁸ who, following rebreathing experiments in men and in animals, noted great slowing of rate, shifting pacemaker, nodal rhythm and progressive delay in A-V conduction. They emphasized the sensitivity of the S-A and A-V nodes to anoxemia but believed that the effect of anoxemia might be an indirect one through the vagus nerves. Resnik,⁷⁹ too, found that the S-A and A-V nodes and auricles were especially sensitive to anoxemia with the consequent slowing of the heart and shortening of the refractory period which predispose to auricular fibrillation.

Another mechanism for production of cardiac irregularity is the *irritability* of the local area of infarction, from which abnormal impulses or reflexes may arise. The area of infarction is a region of diminished blood supply, dying muscle and surrounding inflammatory reaction. As Condorelli⁸⁰ and Froment⁸² have emphasized, it is a question whether the dying muscle or the surrounding inflammatory tissue acts as the irritable focus for the initiation of ectopic beats. Not only may the area of infarction initiate abnormal impulses but it may also interfere with the orderly conduction of the excitation wave through the ventricles. Further, abnormal *reflexes* may arise from this irritable focus either directly or as a result of anoxemia. The importance of the *vagus nerve* in these reflexes was demonstrated by Greene and Gilbert⁷⁸ who were able to abolish the arrhythmias due to anoxemia in dogs by cutting the vagus nerve. Some authors,^{55, 62, 81, 82} finding ventricular tachycardia commonly associated with septal infarction, have suggested that damage to the septum and conduction system as well as local irritability are necessary for the production of ectopic rhythms of this type.

The importance of the various factors discussed above is appreciated when it is realized that, except in complete heart block, there is no correlation between the exact site of thrombosis or infarction and the type of arrhythmia. Since the right coronary artery supplies the A-V node and the bundle of His in 90 per cent of cases and the auricles and S-A node in 60 per cent of cases (Gross⁸³), one would expect that occlusion of this artery would produce bradycardia, nodal rhythm, various degrees of auriculoventricular heart block and auricular fibrillation, flutter or tachycardia, and that the occurrence of these complications would be infrequent with closure of the left coronary artery which supplies the auricles in 20 to 40 per cent of cases and the A-V node rarely. Yet all these arrhythmias, except complete heart block, occurred as often with occlusion of the left as the right artery. When heart block was present, the right coronary artery was almost always

involved, both in our cases and in those reported in the literature ^{44, 68} In the occasional cases in which thrombosis of the left anterior descending artery was associated with heart block, it is possible that this vessel and not the right coronary supplied the junctional tissues or that the right coronary artery was already markedly sclerotic and stenosed and that the greater part of the circulation to the junctional tissues had been supplied by anastomotic vessels from the left coronary artery

In recent discussions, the relationship of *heart failure* to arrhythmias, particularly auricular fibrillation, has assumed a prominent place Luten ^{81, 85} stated that the tachycardia which occurs in heart failure is a compensatory mechanism and that auricular fibrillation, when it occurs, usually is secondary to and not the cause of heart failure He believes that in the presence of auricular damage, dilatation and stretching of the auricular wall from increased intraauricular pressure in ventricular insufficiency is the predisposing factor in the production of auricular fibrillation The same explanation could be applied to auricular flutter and auricular tachycardia Vaquez ⁸⁶ and Nahum and Hoff ⁸⁷ also thought that auricular distention was responsible for the frequent association of auricular fibrillation and heart failure

In a number of cases we have been able to study the validity of this mechanism of heart failure and auricular distention in coronary thrombosis (table 3) We have already found ⁶⁹ that heart failure occurs in the

TABLE III
The Relation of Auricular Fibrillation to Heart Failure in Coronary Thrombosis

Case	Day of Attack	Rhythm	Ventricular Rate	Circulation Time—Sec	Venous Pressure—cm	Vital Capacity—c c	Clinical Heart Failure	
							Left	Right
1	1	Aur fib	110	15	6	2700	0	0
	3	R S R	80	13	5	2600	0	0
2	2	Aur fib	110	31	12	1750	+++	++
	14	Aur fib	100	22	4 5	2300	+	0
3	1	R S R	75	17		2700	±	0
	12	R S R	75	23		2800	+	0
	21	Aur fib	150	34			+++	+
	22	R S R	85	29		1600	++	+

majority of patients with coronary thrombosis Infarction and failure of the ventricles place a strain on the auricles which dilate Auricular dilatation may be seen experimentally and is also suggested by the appearance of large P-waves in the electrocardiogram ⁸⁸ While most of our cases of auricular fibrillation and paroxysmal tachycardia were associated with heart failure, fibrillation occasionally occurred when there was no clinical evidence

of failure or when objective tests, such as the circulation time, indicated only a mild degree (Case 1). Sometimes, auricular fibrillation persisted when heart failure had entirely or largely disappeared (Case 2). Yet, in several instances, even with rapid ventricular rate it spontaneously remitted to normal rhythm in the presence of unchanged or increasing failure (Case 3). This was true in eight of the nine cases with paroxysmal tachycardia. One patient who entered the hospital with definite failure following coronary occlusion developed auricular fibrillation with rapid ventricular rate on the fourth day. During the next 24 hours the failure became advanced and the patient died the following day, yet the arrhythmia spontaneously gave way to sinus tachycardia the day before death. In addition, many of our severest cases of heart failure were associated with regular sinus rhythm. Hence we believe that although heart failure with dilatation of the auricles probably exerts an important influence in the initiation of arrhythmias in coronary thrombosis, many other factors come into play.

Since thrombosis always occurs in patients with diseased coronary vessels, chronic pathological changes which may be significant in the onset of an arrhythmia are usually coexistent. Further defective nutrition of this diseased heart muscle consequent on infarction may produce irregularities. Because of the hypertension so commonly found in coronary thrombosis, especially in patients with arrhythmias, myocardial fibrosis is particularly marked. Moreover, hypertension itself may predispose to arrhythmias. Coronary artery disease alone has not been considered a significant etiological factor in the permanent type of auricular fibrillation in non-valvular heart disease, but rather hypertension^{32, 75}. Brown⁷⁵ found that in coronary artery disease auricular fibrillation was rare unless preceding hypertension was present. No specific pathologic lesion has been found in the auricles even in permanent fibrillation and frequently, no lesion at all^{32, 74, 89}. It seems reasonable to assume that such is the case following acute coronary occlusion.

Ventricular tachycardia deserves special comment. Its rarity in coronary thrombosis in man is in marked contrast to its frequency in experimental coronary ligation⁶⁻¹². Experiments in dogs have emphasized unduly the significance of this arrhythmia with the result that single case reports⁴⁶⁻⁵⁹ have been considered worthy of publication, thus centering attention on the association of coronary artery thrombosis with ventricular tachycardia. Actually, it is one of the rarest of the arrhythmias and occurs only once in several hundred cases. It should be remembered that experimental ligation produces a sudden change in an animal with normal arteries while in man the occlusion caused by coronary thrombosis is gradual and accompanied by compensatory anastomoses produced by previously sclerotic vessels. In the majority of instances in which ventricular tachycardia has been observed in coronary thrombosis it has followed administration of digitalis^{42, 49, 82, 90, 91}. This is doubtless more than a coincidence since digitalis increases the irri-

tability of the heart muscle and in coronary thrombosis where irritability is already great, it may act as a predisposing factor. In fact, during the past few years since the danger of digitalis in infarction has been recognized and the drug withheld, ventricular tachycardia has become very uncommon. However, as Gallavardin and Froment^{61, 62} have suggested, when ventricular tachycardia occurs in a middle-aged patient, coronary artery thrombosis is to be considered a likely diagnosis.

We have already stated that the majority of arrhythmias appear within the first three days of the coronary occlusion and spontaneously remit within 24 to 36 hours. This early appearance of the irregularities can probably be attributed to the fact that in the first few days the pathological and physiological changes are most acute and their ephemeral character probably depends on the subsidence of the acute process in the heart muscle and the improvement in the general circulation of the body. Disappearance of edema adjacent to the infarcted area which may be the site of origin of arrhythmia, may lead to rapid resumption of normal rhythm. The enlargement of anastomotic channels already present or the development of new ones is another possible factor in the short duration of the arrhythmias. It has been suggested^{38, 44, 68} that in heart block the diffuse anastomosis around the A-V node between the left and right coronary arteries^{92, 94} may prevent the development of the arrhythmia or prevent it from becoming permanent.

PROGNOSIS

Diversity of opinion exists concerning the prognosis of auricular fibrillation in coronary thrombosis. Christian¹⁷ states "In my experience those patients developing fibrillation have shown a better prognosis than others." Parkinson and Campbell⁷⁴ maintain that auricular fibrillation has no effect on the clinical course and Levine²² found no influence on the mortality rate. Yet Bedford⁹⁵ states that auricular fibrillation adds to the risk of an attack, although it does not preclude recovery, and seven of Howard's²⁷ 10 patients with auricular fibrillation died. Padilla and Cossio⁹⁶ also believe that it is of prognostic significance. Half of our cases with auricular fibrillation ended fatally, a mortality rate more than double that in patients with normal rhythm.

Auricular fibrillation occurred most frequently in severely ill patients with an advanced degree of heart failure. How significant the fibrillation itself was in the outcome of the attack is problematic since the irregularity usually lasted but a short time and in half the fatal cases death occurred some time after the cessation of arrhythmia. Furthermore, as we have already pointed out, the transitory fibrillation also occurred in patients with little or no heart failure whose condition steadily improved. It would seem, then, that the importance of auricular fibrillation as a prognostic factor is determined largely by the degree of shock and heart failure present at the

time. However, if a rapid ventricular rate persists, the arrhythmia itself becomes a factor in the fatal issue by increasing the degree of shock and failure. In previous reports^{69, 97} we expressed the opinion that heart block alone of the arrhythmias altered the prognosis of the attack, further experience with a larger series makes it apparent that auricular fibrillation, too, is of serious import.

The conclusions regarding auricular fibrillation also apply to auricular flutter. Yet, in spite of a rapid ventricular rate comparable to that in auricular fibrillation, auricular and nodal paroxysmal tachycardia did not affect the outcome of an attack adversely. Only two of our eight patients died. Although the number of cases is too small to generalize it is probable that the low mortality is explained by the fact that the arrhythmia in seven of the eight patients was of short duration.

Premature beats even when multiple were not of importance unless both auricular and ventricular beats occurred together. But here again, the number of cases is too small to permit conclusions to be drawn. However, most authors have found premature beats of little importance although a few^{12, 66, 103} speak of the inherent danger of multiple ventricular premature beats developing into ventricular tachycardia or fibrillation. Such an association occurred only once in our series.

Complete heart block has been recognized as a very serious irregularity. Karsner¹⁶ states that it usually ends fatally, a fact borne out by the high mortality rate in most of the reported cases and in our series in which it was 80 per cent. However, in occasional instances, recovery does take place, and indeed Schwartz⁴⁴ states that 11 of his 15 cases with Stokes-Adams syndrome due to complete heart block survived the acute attack of thrombosis. The high mortality in complete heart block is undoubtedly associated with the marked bradycardia. In three of our four fatal cases the rate remained below 40 until death. In contradistinction, in both Levine's²² and our own series, partial heart block had no effect on the prognosis. In our three cases the ventricular rate was 50 or more, no Stokes-Adams symptoms occurred and none died.

Since only one case with very fleeting ventricular tachycardia was encountered in our entire series, we are unable to discuss this arrhythmia from personal experience. It has generally been considered a very serious complication. About three-fourths of the cases of coronary artery thrombosis with ventricular tachycardia reported in the literature⁴⁶⁻⁵⁹ ended fatally. The gravity of this arrhythmia may lie in the fact that it usually occurs in patients with severely damaged hearts and large infarcts and that it tends to remain more persistent than other forms of paroxysmal tachycardia.

TREATMENT

Since arrhythmias in coronary artery thrombosis are usually transitory and remit spontaneously, specific therapy, such as *digitalis administration*

advocated by some authors^{13, 21} is not routinely necessary. The general measures employed in coronary thrombosis will usually suffice. These measures which we have fully described in previous articles⁹⁷⁻¹⁰⁰ include meticulous care of the diet, absolute quiet and sedation, particularly with morphine. During the first few days the diet consists of small portions of soft food totalling several hundred calories during the day. Such a regime reduces the work of the heart and avoids gastro-cardiac reflexes. If the condition of the patient improves, the caloric intake is rapidly raised to 800 calories and is maintained at this amount for two or three weeks or more. Fluids are restricted to 1200 c.c. during this period. The first week or two visitors are not allowed and the patient is fed by the attendant. Under this treatment pain usually disappears after the first or second day and the patient is comfortable. When heart failure, frequently present soon after the attack, increases, diuretics such as mercururin are employed and oxygen if there is cyanosis or dyspnea. We believe, as do most authors,^{22, 42, 101, 102} that digitalis is contraindicated in the first weeks following coronary artery thrombosis. It not only increases the work of the heart but there is a great deal of evidence^{42, 90, 102} that it initiates or prolongs arrhythmias, particularly ventricular tachycardia and auricular fibrillation, when infarction exists. It is possible that the rarity of ventricular tachycardia in our series was associated with the avoidance of this drug. However, in the occasional cases in which auricular fibrillation with rapid ventricular rate persists and increasing heart failure or shock is present, the administration of digitalis may be necessary. Usually one may wait 24 to 36 hours before giving the drug but this will depend on the individual case.

Although we avoided the use of digitalis as a rule, six patients with auricular fibrillation or flutter did receive the drug through error. In three, it was given after the onset of the arrhythmia, two of these died suddenly before the arrhythmia ceased and in the other, fibrillation became permanent. The remaining three cases received digitalis before the onset of the irregularity and one died. In these cases, therefore, digitalis did not prevent or abolish the arrhythmia.

Since Levine^{22, 48, 60, 63} advocated *quinidine* for ventricular tachycardia in coronary thrombosis its use has become very common^{42, 62, 91}, in fact, the prophylactic administration of this drug soon after the onset of the attack to prevent ventricular tachycardia and fibrillation has been advised^{60, 66, 103} particularly if premature beats are present. However, the rarity of ventricular tachycardia in coronary artery thrombosis makes it seem inadvisable to give routinely a drug which may be dangerous. Even if ventricular tachycardia should set in, it may be transitory, as in our single case, or may respond to morphine. If, on the other hand, it persists and heart failure increases, quinidine should be given in sufficient dosage⁶⁰. The intravenous administration should be employed only if the condition is urgent, when it should be given cautiously, that is, slowly and well diluted.⁶³

Auricular and nodal tachycardia almost always remit spontaneously or after the use of morphine. However, if the rapid ventricular rate is associated with increasing failure, in spite of the morphine, quinidine or digitalis should be given. In one of our cases nodal tachycardia ceased after 54 grains of quinidine, however, the patient died of a cerebral embolus four days later.

Levine²² and Schwartz⁴⁴ have advised the use of *adrenalin* when the Stokes-Adams syndrome complicates complete heart block. In spite of the danger of adrenalin in coronary artery thrombosis, this drug should be tried cautiously, because this condition is so serious and without treatment frequently ends fatally. Schwartz reported good results in his cases.

SUMMARY

In this paper we have presented the conclusions drawn from our study of the arrhythmias occurring in 300 cases of coronary artery thrombosis and reviewed the literature pertaining to the subject. Women were almost twice as prone as men to cardiac irregularities.

All types of irregularities were present. Premature beats found in one-fourth of the patients were the most common, but were of little prognostic significance. Other arrhythmias occurred 46 times in 42 patients (14 per cent). Of these, auricular fibrillation comprised one-half. Ventricular tachycardia was rare, occurring only once. There were eight cases of auricular or nodal tachycardia, five of complete and three of partial heart block. In some instances several arrhythmias developed in the same patient.

The arrhythmias may occur at any time but they usually appeared during the first three days following an occlusion. With the exception of nodal rhythm and heart block which may last one to two weeks, they were transitory, more than half remitting spontaneously within 24 hours.

The mortality rate of the patients with a significant arrhythmia, that is, any arrhythmia other than premature beats, was 39 per cent, while for those with regular sinus rhythm it was 22 per cent. This high mortality rate was attributed to the underlying cardiac enlargement, heart failure and hypertension. Half the deaths occurred after the cessation of the arrhythmia. Only very rarely was the arrhythmia itself the cause of death. Half the patients with auricular fibrillation and flutter, and four-fifths of those with complete heart block died, whereas the patients with paroxysmal tachycardia, nodal rhythm and partial heart block usually survived.

The cardiac rate, whether or not the rhythm was regular, was a very significant factor in the outcome of an attack. If the ventricular rate was above 120 or below 40 beats per minute the outlook was poor, when a rate between 60 and 100 was maintained, the patient almost always recovered.

An arrhythmia may be the first and only sign of coronary artery thrombosis, pain being absent or minimal, in fact, the sudden onset of an arrhythmia should suggest the diagnosis of coronary occlusion. On the other hand,

an arrhythmia with rapid ventricular rate may lead to shock and heart failure which may simulate another coronary occlusion

A number of factors probably play a rôle in the initiation of the arrhythmias heart failure with its associated dilatation of the auricles, anoxemia of the myocardium, nutritional or metabolic disturbances and impulses or reflexes originating in and around the infarcted area. Indeed, it is surprising that arrhythmias are not more frequent. Their relative rarity is probably the result of the copious anastomoses throughout the heart, particularly around the A-V node and septum.

Coronary thrombosis is rare when auricular fibrillation is present.

Heart block alone was associated with a specific anatomical lesion in the heart, that is, posterior wall infarction due to right coronary artery occlusion. In the other arrhythmias both the left and right coronary arteries and both the anterior and posterior surfaces of the left ventricle, were involved with equal frequency. The site of acute infarction or chronic fibrosis does not determine the type of cardiac irregularity.

Because the arrhythmias usually remitted spontaneously after a short period we considered specific treatment unnecessary, either prophylactically or after the onset. In fact, digitalis and quinidine are considered dangerous in the treatment of coronary artery thrombosis since they may actually initiate arrhythmias. The rarity of ventricular tachycardia in our series may be due to the fact that digitalis was not used routinely. Only when a persistent arrhythmia produces severe shock or increasing heart failure should they be given. At the onset of an arrhythmia morphine may be administered liberally. Adrenalin should be used in heart block but only when a severe Stokes-Adams syndrome occurs.

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THE SURGICAL TREATMENT OF PEPTIC ULCER *

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SINCE Billroth, following his successful removal of a carcinoma by pylorotomy in 1881, directed his efforts to the cure of peptic ulcer by surgical measures, a voluminous literature, both medical and surgical, has been accumulated. It is now the consensus of opinion that the problem of the treatment of peptic ulcer is primarily a medical one, assuming surgical significance only with its complications, sequelae and intractable chronicity. The aim of treatment has been to secure a healing of the ulcer or its eradication with a correction of the pathological defects caused by it, together with the institution of such measures as in the light of knowledge and experience are believed to be of value in the prevention of recurrence. In the many types of operations that have been employed, the underlying considerations have been to bring about, as far as possible, a restoration of physiological function, free drainage of the stomach and a partial neutralization of stomach acids by intestinal alkalies.

The occurrence of perforations, bleeding, and malignant degeneration in ulcers left behind, has led to the conviction of the desirability of destroying or removing the ulcer or ulcers in addition to meeting these indications. The wide variation in the degree and character of the lesions encountered in peptic ulcer is such that no single operation suffices to meet the indications in all cases. The attainment of success in its surgical treatment is largely dependent upon three factors: choice of operation, selection of cases for operation, and efficient pre- and post-operative medical management.

For the purpose of discussion, the operative procedures with which we have had personal experience may be classified as conservative and radical. The conservative operations comprised, (a) local excision with cautery or knife followed by suture, (b) local excision plus gastro-enterostomy or pyloroplasty, (c) gastro-enterostomy or pyloroplasty alone. The radical operations consisted in the removal of the ulcer-bearing area by the Billroth I, Billroth II, Polya modification, or sleeve resection methods.

In making a choice of the type of operation to be employed in a given case primary mortality and end results must be the chief considerations. It is obvious that where resistance and vitality have been lowered by long continued disease, marked pyloric obstruction with dehydration and toxemia, inadequate nourishment or continued blood loss, the pre-operative administration of fluids, glucose and blood transfusions are essential in the preparation of the patient for operation, and it is equally obvious that the safety of the patient will be enhanced by the selection of the simplest operation compatible with the correction or alleviation of the pathologic condition.

* Presented at the St. Louis meeting of the American College of Physicians, April 20, 1937.

presented While the roentgen-ray is an invaluable aid in diagnosis, the extent of the local lesion will be revealed by ocular inspection only Quiescent ulcers will permit safer attack than those showing evidence of activity

Perforation into the free cavity or into adjacent viscera, fixation of the duodenum, pylorus and stomach, the presence of inflammatory exudate, recent or calloused, obstruction due to cicatricial contraction, exudative or massive adhesions, location and number of ulcers in varying combinations present problems that are most satisfactorily solved by the selection of that operation best suited to the given case The clinical observation that 90 per cent of gastric ulcers occur at or near the pylorus and along the lesser curvature led Rodman to advocate the resection of the ulcer-bearing area when dealing with ulcers in this location Time and experience have demonstrated the wisdom of this procedure particularly when the ulcers are of the calloused variety Finally a consideration influencing the choice of operation is the efficacy of large resections in the reduction of gastric acidity The observation that following resection of the ulcer-bearing area of the stomach there is a lowering of gastric acidity, and further, that freedom from recurrence is the rule (to which, however there are exceptions), has led to the assumption in some quarters that where there is no acid there will be no ulcer On this hypothesis Finsterer and his followers have practiced the ablation of the acid-bearing portion of the stomach regardless of whether the ulcer be duodenal or gastric, with the avowed intention of producing anacidity We have had no experience with such massive resections other than when necessitated by the location and character of the ulcer, believing the magnitude and extent of the operation to be prohibitive when compared with the favorable results obtained by simpler and less dangerous procedures Furthermore, the presence of hydrochloric acid is essential to the proper physiological action of the stomach and its continued absence, howsoever produced, may be the forerunner of serious secondary disease

The selection of the type of operation to be employed is, and should be, the concern of the surgeon the selection of the case for operation should be the joint concern of the internist and the surgeon While unanimity of opinion is not yet to be obtained, accumulated experience and knowledge permit fairly definite indications for operative treatment The three indications upon which all agree are perforation, hemorrhage, and obstruction

Immediate closure of an acute perforation is the essential indication Approximately 80 per cent of the acute perforations of duodenal ulcers occur on the anterior wall, and 90 per cent of the acute perforations of stomach ulcers occur on the lesser curvature of the prepyloric portion perforation on the posterior wall is frequently sealed by adhesion of adjacent structures Closure of the opening with superimposed layers of Lembert sutures and an omental fat graft suffices not only to control leakage but in a goodly percentage to secure healing of the ulcer as well The employment of additional measures, such as excision or cauterization of the ulcer, py-

loroplasty, gastro-enterostomy or resection of stomach will depend upon the extent, character, and location of the local lesion and the general condition of the patient. The prime consideration in such catastrophes is the saving of life. This is accomplished by the stoppage of the leak. It may be stated as a general rule that the greatest safety to the greatest number prohibits doing more, yet, in the presence of marked pyloric or duodenal obstruction, granting that the condition of the patient permits, a pyloroplasty or gastro-enterostomy may be done with reasonable safety, thus giving assurance of permanent relief and obviating a second operation. If the perforation occurs in a calloused ulcer on the lesser curvature, the infiltration surrounding the ulcer may not only prevent suture but may arouse the suspicion of malignancy as well, in which event excision or gastric resection will be indicated, as the condition of the patient and the judgment of the operator dictate. Perforations in which more or less successful efforts at closure have been made by nature are observed in three clinical groups: one, rather extensive epigastric peritonitis with subhepatic or subphrenic abscess, two, localized peritonitis with recent inflammatory exudate matting together structures adjacent to the perforation, and, three, chronic perforations in which the acute inflammatory phenomena have disappeared and the perforations remain sealed by close adherence of adjacent tissues. In the first two groups, the perforation itself, surrounded and sealed by acutely inflamed tissues, will neither demand attention nor permit surgical attack, the operative treatment consisting in the first group of drainage of the purulent deposits and in the second of gastro-enterostomy. In the third group the location of ulcer and the nature of the structures to which it has adhered will determine the nature and extent of the operation.

Hemorrhage in both gastric and duodenal ulcers occurs in approximately 25 per cent of all cases, appearing usually in one of three forms: (1) More or less constant seepage sufficient to produce anemia, (2) single or recurring hemorrhages of appreciable amount as hematemesis or melena and (3) massive bleeding, which immediately threatens the life of the patient. Ulcers that show constant seepage and recurring hemorrhage of appreciable amount which continues in spite of appropriate medical treatment should be subjected to operation. The type of operation employed should include the destruction of the ulcer, since such ulcers, when treated by conservative operations which do not include their eradication, show in many instances a definite tendency to further bleeding. The treatment which we have employed for massive hemorrhage consists of rest in bed, physiologic rest of the stomach, fluids and nutrition in the form of glucose administered by rectum, subcutaneously, and intravenously, the exhibition of coagulants, chiefly fibrogen by mouth and subcutaneously, and whole blood transfusions. Under this regime the bleeding as a rule will cease, permitting of further study of the patient and a decision for or against operation based upon the associated symptoms, history and laboratory findings. Occasionally a case

will be met in which such measures fail, in which the necessity of controlling the bleeding becomes an indication for immediate operation

The patients with duodenal ulcers that we have selected for operation have presented one or more of four conditions (1) Perforation, both acute and chronic, (2) repeated or long continued hemorrhage, (3) pyloric obstruction, (4) and marked chronicity. A single massive hemorrhage is not regarded as an indication for operation, and in such cases in the absence of the remaining conditions the chance for healing under medical treatment should be afforded until further bleeding or chronicity demonstrates its futility. Chronicity in spite of appropriate medical treatment is accepted as a failure of the latter and an indication for operation. For some unexplained reason duodenal ulcers do not show a tendency to malignant degeneration, hence it has been argued that chronicity alone does not justify resort to operation. The danger of perforation, the menace of hemorrhage, the possibility of obstruction and the continued discomfort produced by the chronic ulcer which proves resistant to an intelligently planned medical treatment afford sufficient grounds to negate this assumption.

The types of operation which we have employed in the treatment of duodenal ulcer are: Excision alone, gastro-enterostomy alone, excision or cautery destruction of the ulcer combined with gastro-enterostomy or pyloroplasty, and resection of the pylorus and duodenum. Resection of the ulcer alone was tried in a small series of cases and abandoned since three patients so treated showed recurrence within a year. Excision of the ulcer with a pyloroplasty, Finney or modified Mikulicz, has been employed for ulcers situated on the anterior wall near the pylorus, showing a minimal amount of duodenal distortion. For the satisfactory performance of this operation it is essential that the pylorus and duodenum be readily mobilized so as to afford opportunity for the necessary manipulation. In the cases conforming to these limitations it has proved a satisfactory procedure.

With increasing experience gastro-enterostomy is less frequently employed alone as the treatment of choice in duodenal ulcer. The destruction of duodenal ulcers is not an imperative indication, but when local conditions make this a feasible and reasonably safe procedure it is advisable in that it at once gets rid of the ulcer, avoiding dependence on a slow healing process, and obviates the possibility of subsequent bleeding and perforation. The eradication of the ulcer is preferably accomplished with the cautery after the method of Balfour. With this technic the bleeding and operative trauma are decidedly less and the destruction of the ulcer just as certain. The cautery wound is closed with Lembert sutures and covered with an omental fat graft, after which a posterior gastro-enterostomy is done. This conservative procedure will meet the indications in the majority of simple duodenal ulcers and the excellent results obtained place the burden of proof upon advocates of other methods to show just cause for such advocacy.

In the presence of obstruction due to cicatrization in the duodenum and pylorus dependent upon ulcer of the duodenum, gastro-enterostomy alone

affords beneficent results, the greater the obstruction the more certain and more complete the relief. Gastro-enterostomy alone is also to be considered where marked periduodenal inflammation has anchored the gut to the liver, and in those cases where age, lowered vitality or obesity contraindicate any direct procedure. When the ulcers are multiple, and they are in from 5 to 6 per cent of cases, when situated on the posterior wall, difficult of access and so calloused as to render healing difficult, and when, so situated, the ulcer has perforated into the head of the pancreas with fixation of duodenum and pylorus to the latter organ, we have come to the practice of resection of the duodenum and pylorus. Ulcers presenting such complicating lesions do not lend themselves to cautery destruction or to excision with pyloroplasty. Our experience with gastro-enterostomy alone in such cases has been disappointing in that persistent gastric discomfort, recurrent bleeding, pancreatitis and pancreatic malignancy have been noted. It is true that the radical operation carries a graver operative risk, but this is justified by the greater assurance of relief.

The indications for the institution of surgical measures in the treatment of gastric ulcers comprise those which apply to duodenal ulcers, namely, perforation, hemorrhage, obstruction and chronicity, to which must be added the danger of malignant degeneration. While malignancy does not become engrafted on chronic ulcer with the frequency which some authors have stated, personal observation has afforded conviction of its occurrence. Patients with frank cancer at the time of examination have given ulcer histories of long duration. Patients upon whom in our earlier experience we had done gastro-enterostomy alone for chronic gastric ulcer have returned years later with gastric carcinoma. This common observation of the tendency of chronic gastric ulcer to undergo malignant transformation would seem to render imperative the destruction or removal of the ulcers in the course of operations undertaken for their relief. The operations with which we have had experience are gastro-enterostomy alone, excision of ulcer alone, cauterization or excision combined with gastro-enterostomy, sleeve resection of the pars media, and resection of the pylorus, antrum, and such part of the pars media as may be necessary to include the ulcer-bearing area. The above mentioned observation of the occurrence of carcinoma in chronic ulcer treated by gastro-enterostomy alone has led us to abandon such conservatism and in the cases selected for this procedure to supplement it with cauterization or excision of the ulcer. In four patients presenting chronic saddle ulcer of the lesser curvature, pars media, a sleeve resection was done. In two of these recurrence was noted and relief obtained by a subsequent gastro-enterostomy. The cases to which the combined procedure of excision or cauterization combined with gastro-enterostomy is applicable are those in which small, resectable ulcers are situated on the lesser curvature, or in the pars media, and also all ulcers situated high on the lesser curvature or posterior wall. Ulcers of the lesser curvature

showing marked inflammatory deposit are best treated by sleeve resection with a gastro-enterostomy, or by pyloric resection, since the defect left by excision or cauterization is such as to render accurate suturing difficult and to produce marked distortion and deformity. Ulcers with a crater of one centimeter or less in diameter are rarely malignant, and are susceptible of conservative treatment, when the craters present larger diameters, the presence of malignancy is to be considered as possible, and unless one feels confident of his ability to distinguish by ocular inspection between simple chronic ulcer and ulcerated carcinoma, or ulcer with beginning carcinoma, the patient should be given the benefit of the doubt and radical treatment employed. Ninety per cent of gastric ulcers occur on the lesser curvature and posterior wall at the pyloric end of the stomach the ulcer-bearing area of Rodman. The presence of inflammatory deposit in the stomach wall around the margin of the ulcer, the presence of perigastric adhesions or of sealed perforation into the liver, pancreas or gastro-hepatic omentum, and the size of the stomach at this point make difficult if not impossible, the employment of conservative excision or cauterization. The probability of failure of healing with a continuation of symptoms and the possibility of perforation, bleeding and malignant transformation, if gastro-enterostomy alone is done, have led to the rather universal acceptance of pyloric resection as the operation of choice in such cases. The Billroth I gives a nearer approach to physiological restoration, when local conditions are such that it can be carried out. In the wider resections the Polya modification of the Billroth II has satisfactorily met the indication.

A proper selection of patients for operation and the use of good judgment in the choice of operation for the given patient combined with dietary and medical supervision for at least one year following operation, offer the sufferer from intractable peptic ulcer, its complications and sequelae an excellent chance for relief. Peptic ulcer may recur after any type of operation, being located at the former suture line or in new locations in the stomach and duodenum, or in the jejunum at or below the site of anastomosis with the stomach. Fortunately, recurrent ulcer is observed in but a small percentage of cases. The cause for recurrence of ulcer is as elusive as that for its primary appearance. Other sources of failure are to be found in faulty operative technic, in leaving behind an infected gall-bladder or diseased appendix, in activation of an unremoved ulcer, in overlooking distant foci of infection, in the resumption of a faulty diet.

Finally, it should be borne in mind that in the vast majority of patients presenting gastric symptoms, the latter are due to causes extrinsic to the gastric tract. Granting the coincidental occurrence of peptic ulcer in such a patient, its treatment is doomed to complete or partial failure in so far as securing freedom from symptoms is concerned, unless the extra-gastric causes of dyspepsia can be eliminated.

REACTION AND SPECIFIC GRAVITY OF THE URINE IN RELATION TO NEPHRITIS (A STUDY OF TEN THOUSAND URINALYSES) *

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INTRODUCTION

A STATISTICAL analysis of over 10,000 urine specimens is presented. Special attention was given to the specific gravity of urines in relation to their reaction and to pathological findings.

Some significant correlations have been discovered which may have important clinical applications, especially with reference to the management of nephritis and allied diseases.

The data involved in this report represent consecutive urinalyses performed in approximately a year's time in an active general hospital. The bulk of the urinalyses were single morning specimens from hospital patients. A small fraction were 24 hour specimens. Less than half were single specimens from out-patients.

The specimens from the hospital wards came from approximately 2,270 patients, about two-thirds of whom were surgical cases. The series therefore represents an average of between two and three urinalyses per patient. The great majority of specimens were from males, an almost negligible number being from a small female ward of the hospital.

A fraction of the urine specimens was obtained from persons in normal health. The majority of the specimens were from patients having a large variety of general medical and surgical disabilities requiring hospital treatment.

In view of the fact that acid urines may become alkaline on standing due to bacterial action, all twenty-four hour specimens were preserved with a crystal of thymol. Single morning specimens and out-patient specimens were examined promptly after their arrival in the laboratory. The number of cases which may have had alkaline urine due to bladder retention was insignificant when compared to the large number of specimens involved in this study.

DATA AND EXPERIMENTAL WORK

It is generally held that the normal human urine is acid in reaction. This is stated by all authorities on physiological chemistry, and is undoubtedly true. Of the urine specimens involved in this study 87.4 per cent were found to be acid.

* Received for publication March 17, 1937.

From the Laboratory Center, United States Veterans Facility, Fort Miley, San Francisco, California.

The urine specimens, from which the data presented herewith were obtained, were carefully tested for reaction with good quality red and blue litmus paper and recorded as alkaline, neutral or acid. The specific gravities were carefully determined and recorded.

Of 10,155 urinalyses it was found that 319 specimens were neutral, 961 alkaline and 8,875 acid (table 1).

TABLE I

	Acid	Neutral	Alkaline
Number of specimens	8,875	319	961
Per cent of total specimens	87.4	3.1	9.5
Mean specific gravity	1.020	1.014	1.013
Probable error of mean	± 0.00005	± 0.00025	± 0.00015
Standard deviation	± 0.0047	± 0.0046	± 0.0048
Range of specific gravity	1.015-1.024	1.010-1.019	1.008-1.018
Pathological specimens	448	29	106
Per cent pathological	5%	9%	11%
Output of solids per liter	52 gm	36.4 gm	33.8 gm

The average specific gravity of the neutral specimens was 1.0141, of the alkaline group 1.0127, and of the acid group 1.0196. The distribution curve of the specific gravity in each of these groups is shown in chart 1.

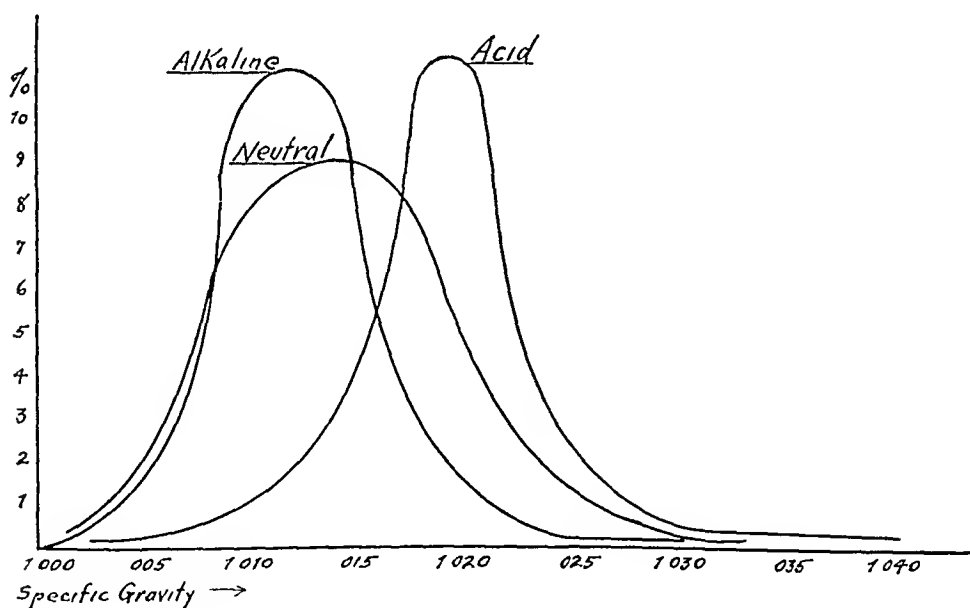


CHART I Distribution of 10,000 urinalyses

There was a difference between the neutral and alkaline averages of 0.0014. The standard error of the difference was ± 0.00029 , making the difference 4.8 times the standard error of the difference.

The difference between the means of neutral and acid groups was 0.0055.

The standard error of the difference was ± 0.00255 . This gave a difference 21.5 times the standard error of the difference.

Between the acid and the alkaline groups there was a difference of 0.0069 with a standard error of ± 0.00158 . Thus the difference is 43.6 times the standard error of the difference.

The above figures are highly significant. They show definitely that there is a correlation between the specific gravity and the reaction of the urine. Statistically speaking, when the difference between the means of two series is over two times the standard error of the difference it is regarded as definite evidence of significant difference, and not due to chance.

It has been found that the specific gravity of acid urines is higher than that of neutral urines, and that of neutral urines higher than the specific gravity of alkaline urines. It has been shown definitely that these differences are not accidental, but that they are due to definite factors causing a correlation between reaction and specific gravity of the urine.

Long's coefficient or Haser's method¹ may be used to determine the output of urinary waste products from the specific gravity of the urine. This is done as follows: Multiply the last two figures of the specific gravity by the coefficient of 2.6. This gives the total solids in one liter of urine. To determine the total solids in the 24-hour specimen multiply the above product by the volume of the specimen in cubic centimeters and divide by 1,000. For example let the specific gravity of the 24-hour specimen be 1.012, the amount 1,200 c.c., then

$$\frac{12 \times 2.6 \times 1200}{1000} = 37.4 \text{ gm}$$

If we assume that the average output of urine is 1,000 c.c. for each of the groups (acid, alkaline and neutral), and apply Long's formula, we find that there will be an average of 52 grams of solid waste matter excreted in the acid group, 36.4 grams in the neutral group and 33.8 grams in the alkaline group.

It may be true in some cases when the urine is alkaline and has a low specific gravity there will be a compensatory increase in the urinary volume. The average 24-hour volume for a series of alkaline urines was 2,066 c.c. For a series of acid urines it was 1,611 c.c. Applying Long's coefficient to these average values we find that the excretion of solids would be

	AVERAGE VALUES		
	Volume	Specific Gravity	Total Solids
Acid	1,611 c.c.	1.020	83.8 gm
Alkaline	2,066	1.013	69.8
Difference	—	—	14.0 gm

Thus it is shown in this series that the average amount of excretory solids of the urine is greater in the acid series than in the alkaline. It must be

remembered that here we are dealing with averages. The values in individual specimens may vary greatly.

This indicates that the ability of the kidney to excrete solids and to concentrate the urine is greater when the urine is acid.

It has been common practice for the physician to prescribe alkalis in the treatment of nephritis. Empirical improvement in such cases has unquestionably occurred following alkaline medication. In view of this fact it was determined to study the effect of an alkaline medium on the formed elements of pathological urines. In order to do this the following experiment was performed *in vitro*.

Acid urines containing casts and usually other abnormal findings as albumin, red and white blood cells, were alkalinized with sodium hydroxide. Sodium hydroxide (10 per cent solution) was added drop by drop to the individual specimens until the specimens gave a permanent pink color to phenolphthalein. This gave a pH about 8.4. The alkalinized urine specimens, containing casts, were then incubated at 37.5° C in a water bath for various periods of time. The findings were as follows:

After three hour incubation the casts were partially dissolved. All casts dissolved in the incubated alkaline urines in four hours or more. When potassium hydroxide was used to alkalinize the acid urines in place of sodium hydroxide, the casts were just as effectively dissolved. Other formed elements, especially red blood cells, tended to disappear also but not to the same extent as casts.

Crystals were not especially studied but seemed to be increased in amount on alkalinizing the acid urines.

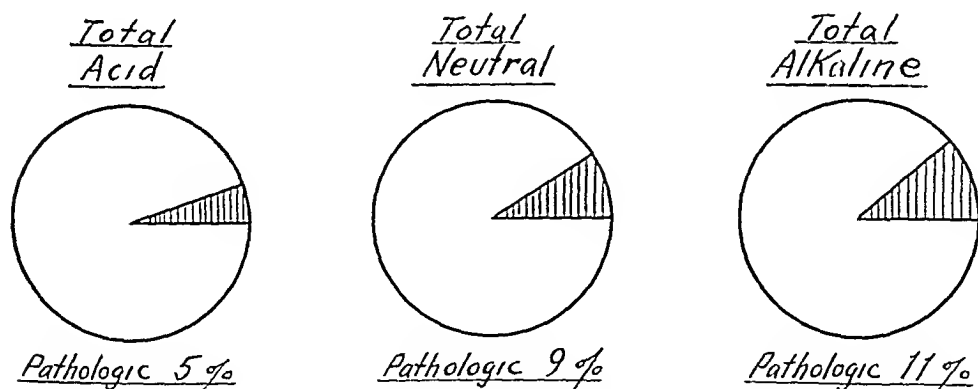


CHART II Incidence of pathologic specimens in 10,000 urinalyses

Further evidence that there is a correlation between kidney disease and urinary reaction has been found. As shown in table 1, 11 per cent of alkaline urines, 9 per cent of neutral urines and only 5 per cent of acid urines were pathological (chart 2). In this study, urines were listed as pathological which contained one or more of the following constituents: sugar, albumin, casts, red blood cells and pus.

TABLE II

Specimen	Specific Gravity	Sugar	Reaction	Acetone
WES 1	1 030	4%	Alkaline	Trace
ROS 2	1 025	—	Alkaline	Trace
CM 3	1 029	—	Alkaline	Trace
RJM 4	1 028	—	Alkaline	Trace
GFL 5	1 035	—	Acid	—
GFL 5a	1 026	Trace	Alkaline	Trace
HK 6	1 029	—	Alkaline	Trace

As shown in table 2 there were six urine specimens in the series which were alkaline in reaction and yet showed traces of acetone. This seemed to be a rather unusual finding and it is not explained nor understood. This phenomenon has been reported before by Schrader². It seems to indicate that ketosis can exist even when there is an excess of alkaline salts in the body and urine.

DISCUSSION

The above findings do not support the practice of prolonged alkalinization for nephritis, especially in those cases where there is retention of uremia, since it appears that the ability of the kidney to excrete solids is greater when the urine is acid. However it has been common practice for the physician to prescribe alkalis in the treatment of nephritis and other urinary infections. More recently the advisability of this practice has been questioned.

Since this matter has come to our attention, we have observed a few fatal cases of uremia. The majority of the urinalyses performed on these cases were alkaline in reaction. It is natural to wonder if there is not some relationship between the poor results and the alkaline condition in such cases.

Steele³ has recently recognized the kidney damage produced by prolonged alkaline medication. The alkalis were administered for the treatment of a patient with a gastric ulcer. On correcting the alkalosis the secretory ability of the kidneys improved. There were no clinical symptoms of alkalosis except the kidney damage, indicating that the kidneys are affected before the clinical symptoms of severe alkalosis appear.

Morgan⁴ fed acid, neutral and alkaline diets to dogs in a study of calcium and phosphorus metabolism. It was concluded, among other things, that renal damage may result from the long continued use of alkaline diets. This important experimental work was discussed in an editorial in the *Journal of the American Medical Association*⁵.

Berger and Binger⁶ report seven cases of alkalosis resulting from alkaline treatment of peptic ulcer. In all seven cases impaired renal function was demonstrated during alkalosis. After the alkalosis had been corrected, evidence of impaired renal function persisted in five of the seven cases, thus indicating that permanent renal damage may result from alkalosis.

In addition to the alkaline medication in cases of advanced nephritis, patients are often given an alkaline diet, consisting usually of fruit juices which further alkalinize the urine ^{7 8 9} Fruits on being ashed yield alkaline salts predominately and are therefore alkaline ash foods

It often happens that patients will continue alkaline self-medication after the physician has advised its discontinuance Many people are known to take alkaline medicines for long or short periods without medical advice It is obvious that such self-medication with alkalis is not without danger The public is being induced to engage in alkaline self-medication by many commercial interests through various popular means of advertising

In view of the evidence that has been accumulating on the harmful effect of prolonged alkaline medication, it is obvious that the above mentioned commercial exploitation of alkaline waters, crystals and drugs is not in the public interest Alkaline medication, like any other medication, should be under the control of the physician The tendency to regard alkaline self-medication as harmless should be combated by the medical profession There is no sound reason why sodium bicarbonate should be a household remedy any more than hydrochloric acid

In view of the above evidence that alkalis diminish the ability of the kidneys to concentrate the urine it would seem necessary to take this into consideration in performing and interpreting tests such as the Mosenthal and other kidney function tests

In spite of the above consideration, the empirical administration of alkalis seems in some cases to have a temporarily favorable effect on nephritis An explanation of this is suggested by some experiments, *in vitro*, reported above In these experiments acid urines which contained casts were alkalinized with sodium hydroxide and after four hours' incubation, the casts were dissolved These findings seem to justify the alkalinization of the urine in cases of nephritis with casts The good effect of the alkalinization is probably due to the solution of casts in the kidney tubules, thus opening blocked tubules Prolonged alkalinization would not appear necessary to accomplish this purpose, inasmuch as casts are dissolved in alkaline urines in about four hours time *in vitro* Prolonged alkalinization is further contraindicated because of the danger of causing alkalosis and kidney damage as shown by various workers

Aside from dissolving casts the administration of alkalis would seem to be contraindicated Many investigators in recent years have shown that acid urines are bacteriostatic and in some cases even bactericidal whereas neutral and alkaline urines are not

THE ACID REGIME IN TREATMENT

The practice of giving acids, acid salts and acid ash foods seems to be indicated in cases of nephritis where there is inadequate excretion of waste products

Acid ash foods (especially meats), have been indicted as etiological factors in the causation of nephritis, but up to the present time, there has been no generally accepted experimental work to show that the acid ash foods and the acid salts which they contain, namely sulphates, chlorides and phosphates, can cause nephritis. On the contrary, evidence has been accumulating to show that acid ash foods and acid salts have a favorable influence on nephritis and on urinary infections.

The acid foods are those which contain an acid ash—meats, game, seafood, fish, eggs, grains, cheese and some nut meats.

Thomas¹⁰ studied the Eskimo during the MacMillan arctic expedition of 1926. He found that the Greenland Eskimo living on an exclusive acid ash diet, consisting entirely of meat, had no increased tendency to vascular or renal disease. On the other hand he found that the Labrador Eskimo who ate cooked meat with many prepared, dried and canned fruits and vegetables was very subject to both vascular and renal diseases.

In 1931 Lashmet¹¹ reported the treatment of nephritic edema by acid. He found that the administration of hydrochloric acid or ammonium chloride decreased the edema while neutral chlorides as sodium chloride, did not. In regard to diet, he found that an alkaline ash intake increased nephritic edema while an acid ash diet decreased the edema.

The above mentioned work of Lashmet, showing that acid medication and acid ash foods reduce nephritic edema is revolutionary to modern medical practice. In the light of evolution, however, it seems physiologically reasonable. Primitive man was nomadic and existed on acid-ash foods almost exclusively, namely, meat, fish and eggs, and later, grains. Thus the human kidney is phylogenetically adapted to excreting acid urine. This tends to class man nearer to the carnivora with acid urinary excretion than to the herbivora which excrete alkaline urine.

Tables of acid ash foods and of alkaline ash foods are available in standard works for those who are interested in this matter. Such lists are given by Sherman¹², Hawk and Bergeim¹³ and by Manville and Winchell¹⁴. The latter give an extensive list which was compiled from several sources.

Those who are interested in the clinical symptoms of alkalosis are referred to a recent article on "Alkali Poisoning" by Cope¹⁵. This author suggests the use of hydrated magnesium silicate in place of soluble alkalis for treating gastric ulcer. An abstract of this work appears in the *Journal of the American Medical Association*¹⁶.

Favorable reports on the treatment of urinary infections with ketogenic diets have appeared. It is suggested that perhaps the good results may have been due to the acid-ash diets used rather than to any ketone bodies that may have been formed.

The inorganic acid salts of acid-ash foods would be more effective in reducing the pH of the urine than the ketone bodies derived from lipoids. Furthermore, it is practically impossible to produce actual ketosis in non-diabetic individuals.

Ketone bodies can be present in alkaline urines. It was found that out of 961 alkaline urines, six showed a trace of acetone (table 2). The specific gravity of these specimens was unusually high for alkaline urines, indicating an unusual excretion of waste products. This phenomenon has been reported previously by Schriader.² No explanation is offered for this comparatively rare phenomenon. However, its occurrence suggests that acidosis and ketosis are separate and not necessarily related conditions. Ketone substances are derived from the incomplete oxidation of fats. Whereas acid substances such as the acid salts (chlorides, sulphates and phosphates) which give the urine its normal acidity, are derived from acid-ash foods of the diet and the catabolism of tissues. The specific rôle of foods in relation to the composition of the urine, has been comprehensively studied by Blatherwick.¹⁷

It is obvious from the foregoing that the inorganic mineral ash of foods does have a definite effect on the body chemistry and has important relationships to disease. Acid ash foods and alkaline ash foods as well as acid and alkaline medicines, deserve extensive further study in this regard.

It appears from this and other investigations that excessive alkaline intake has a deleterious effect upon the kidneys and that this effect can appear before symptoms of clinical alkalosis develop.

SUMMARY AND CONCLUSIONS

1 The ability of the kidney to excrete solids and to concentrate the urine is greater when the urine is acid than when it is alkaline or neutral.

2 Acid urines show fewer abnormal findings than alkaline and neutral urines.

3 Prolonged alkalinization of the urine apparently produces kidney damage.

4 Temporary alkalinization of the urine is apparently of service in dissolving casts and thus opening blocked kidney tubules.

5 Alkaline self-medication should be discouraged.

6 Alkaline medication, as well as acid medication, should be controlled by the physician.

7 Acid types of therapy may prove superior to alkalinization in the treatment of nephritis and its complications as well as in other urinary infections.

8 A definite correlation has been demonstrated between the reaction of the urine and its specific gravity. Acid urines generally have a higher specific gravity than alkaline or neutral specimens and therefore remove more waste products from the body.

The authors wish to acknowledge the technical assistance of Mr. Dale B. Frost, who performed the urinalyses which furnished the data for this paper.

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PROBLEMS CONNECTED WITH THE USE OF PROTAMINE-ZINC-INSULIN *

By HENRY T RICKETTS, M D , *Chicago, Illinois*

THE efficacy of protamine insulin in the treatment of diabetes has been convincingly demonstrated by a number of workers ^{2 3, 6, 9, 11, 12, 13, 14, 15, 18, 19} during the past year. Its superiority over the old insulin as evidenced by better control of the blood sugar, fewer reactions, reduction in the number of daily injections and often an appreciable saving in total requirement cannot be doubted.

All investigators † have recognized, however, that the slow and prolonged action to which protamine insulin owes its conspicuous advantages is also responsible for certain difficulties peculiar to its use. It seems appropriate at this time, therefore, with the new material recently placed on the market, to report an additional series of cases with the specific purpose of redirecting attention to these problems and outlining methods of meeting them.

This study is based on experiences with the administration of protamine insulin to 26 diabetic patients. Of these, five were children. The disease was classified as severe in 12 cases, moderately severe in nine and mild in five. Of 20 patients who were first given protamine insulin in the hospital, 19 were transferred from regular insulin and one patient was treated with the protamine compound alone. In all of the hospitalized cases several determinations of the dextrose content of the blood and urine were made daily, usually before breakfast and from three to four hours after each meal. Of the six patients who were first given protamine insulin in the out-patient department, four had been taking regular insulin and two had received none.

One house physician was forced to return to regular insulin before he had become stabilized because of marked hyperglycemia alternating with severe reactions which interfered with the performance of his duties. Another patient was carried through pregnancy with protamine but was given regular insulin alone at delivery and for four weeks thereafter in the fear that the action of the former might prove too slow and inflexible to meet the rapid fluctuation in tolerance incident to parturition and lactation. With these two exceptions no patient who has started the use of the new insulin has discontinued it, and all but one have returned at frequent intervals for analyses of the blood or urine or both.

* Read in part before the Chicago Society of Internal Medicine, February 22, 1937.

From the Department of Medicine of the University of Chicago.

The author is indebted to Dr. Walford Swanson for the privilege of studying five children in the Bobs Roberts Memorial Hospital, and to Dr. Maurice Glock, Miss Vivian Iob, Miss Mabel Egan and Miss Louise Klein for numerous determinations of the blood sugar.

For the sake of simplicity the term "protamine insulin" will be used in place of protamine-zinc-insulin except where otherwise indicated.

† See especially the communication by Allen ¹

Because of the great advantage in convenience an effort was made, successfully in all but one case,* to control the blood sugar by a single daily injection of protamine insulin given an hour or so before breakfast, either alone or in combination with a small, simultaneous dose of regular insulin. The following remarks apply particularly to this form of administration.

It should be stated in all fairness that the accompanying charts represent juvenile or relatively severe adult diabetics whose management by any method would not be easy, and they have been chosen for presentation here because they illustrate the difficulties with which any physician undertaking treatment with protamine insulin may have to contend. In the milder cases of the present series, as in other reported series, good results were obtained with much less effort.

HYPERGLYCEMIA AFTER MEALS WITH NORMAL OR LOW BLOOD SUGARS DURING THE NIGHT

The difficulty most commonly encountered in the use of protamine insulin is that, particularly in severe cases, what appears to be the proper dose leads to marked post-prandial hyperglycemia though the blood sugar during the night or in the early morning may be normal or even subnormal (figure 1, July 21, 22, figure 2, June 5, 8, figure 3, Jan 18, 21, 24, figures 4 and 5). Simply increasing the dose in an attempt to take care of the carbohydrate of the meals is apt to result in further hypoglycemia the following morning or before (figure 3, Jan 18, 19, 24, 25, 26). In such a dilemma several courses are open.

(a) The time of administration of the protamine insulin may be pushed back to two or more hours before breakfast. This is inconvenient and in our experience has rarely been satisfactory.

(b) The dietary carbohydrate may be redistributed, one-fifth of the day's allowance being given for breakfast, two-fifths for lunch and two-fifths for supper. Indeed, it has been our recent practice to arrange the diet in this manner on the first day of treatment rather than waiting until the necessity for the change becomes apparent. Such a distribution imposes less of a burden on the slowly acting insulin soon after it is injected, reserving the greater demands for a time when its hypoglycemic effect is well under way, and constitutes a logical basis for the further adjustment of food and insulin which is often necessary.

With the diet apportioned as above and with a given dose of protamine insulin, the patient may react in one of several ways.

1 Control of the blood sugar may be good throughout the 24 hours.

2 The fasting blood sugar may be normal but hyperglycemia still occur after some of the meals. In this event the dose of protamine should not be altered, but a further redistribution of carbohydrate must be made. We have been surprised at what small changes sometimes accomplish the desired result.

*This patient required two daily injections of protamine-calcium-insulin. It has not been possible to rehospitalize her for trial with the material containing added zinc.

In the case of R B (figure 1, July 22, 23), for example, the subtraction of only 5 grams of carbohydrate from breakfast and its addition to supper spelled the difference between poor and good control. Since the fasting blood sugars on July 21 and 22 were already normal, the slight increase in the dose of protamine on the

Effect of small changes in insulin dosage and carbohydrate distribution

Later, increase in insulin requirement and instability

Irregular hypoglycemia, often without symptoms

RB 149875, Age 6, Sex M, Duration ± 6 mo

Diet, C $\frac{130}{123}$ P $\frac{90}{82}$ F $\frac{142}{129}$

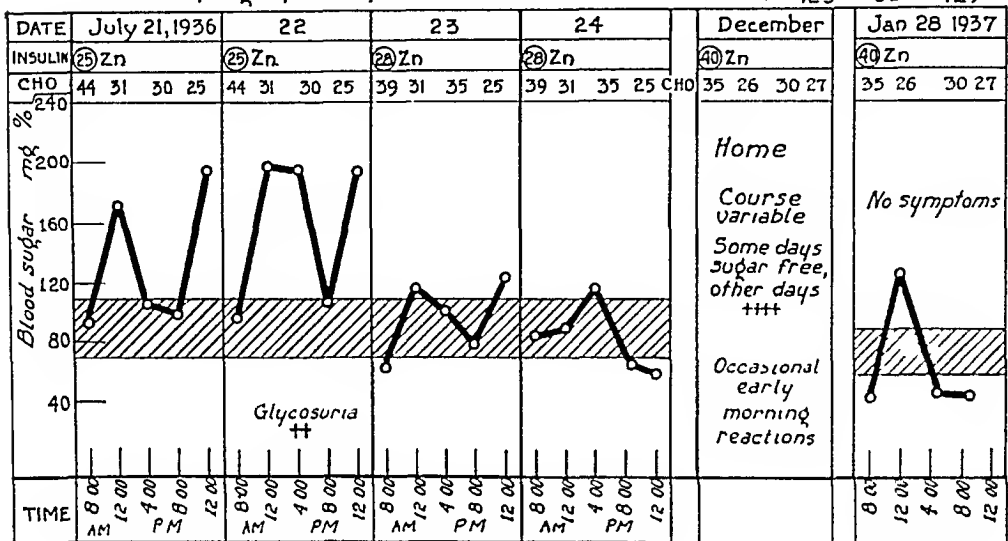


FIG 1 Protamine-zinc-insulin is indicated by figures within circles followed by "Zn". Regular insulin in succeeding charts is shown by figures without circles. The third line shows the distribution of dietary carbohydrate (not total glucose value) between breakfast, lunch, supper and bed time. The shaded area represents the average normal range of blood sugar for the method used. In this case post-prandial hyperglycemia was well controlled by small changes in carbohydrate distribution and dosage of protamine insulin. The dose, however, need not have been increased since the blood sugar during fasting was already normal. Note symptomless hypoglycemia on Jan 28, when the blood sugars were obtained in the out-patient department.

twenty-third and twenty-fourth was probably superfluous and, indeed, led to mild hypoglycemia.

The case of A F (figure 2) is similar. The division of carbohydrate in the proportion of 20-40-40 on June 6 resulted in hypoglycemia before lunch. On June 8 the ratio of 30-40-30 was unsatisfactory. The mean of 25-40-35 reached on June 10, however, gave adequate control throughout the day.

In principle, obviously, carbohydrate should be deducted from the meal following which hyperglycemia occurs, and added to the meal following which the blood sugar is low. Our experience with patients who are sensitive to such small shifts in carbohydrate is at variance with that of other writers^{9, 12, 13, 18}, who imply that with protamine insulin considerable latitude in diet is permissible.

3 The fasting blood sugar may be too low, with or without glycosuria

during the day In this case, either (1) the dose of protamine must be reduced until the morning blood sugar is normal, any resulting daytime hyperglycemia being cared for by dietary adjustment, or (2) the dose of protamine may be kept the same and a bed-time feeding of 10 to 30 grams of carbohydrate given If glycosuria occurs after meals, the bed-time carbo-

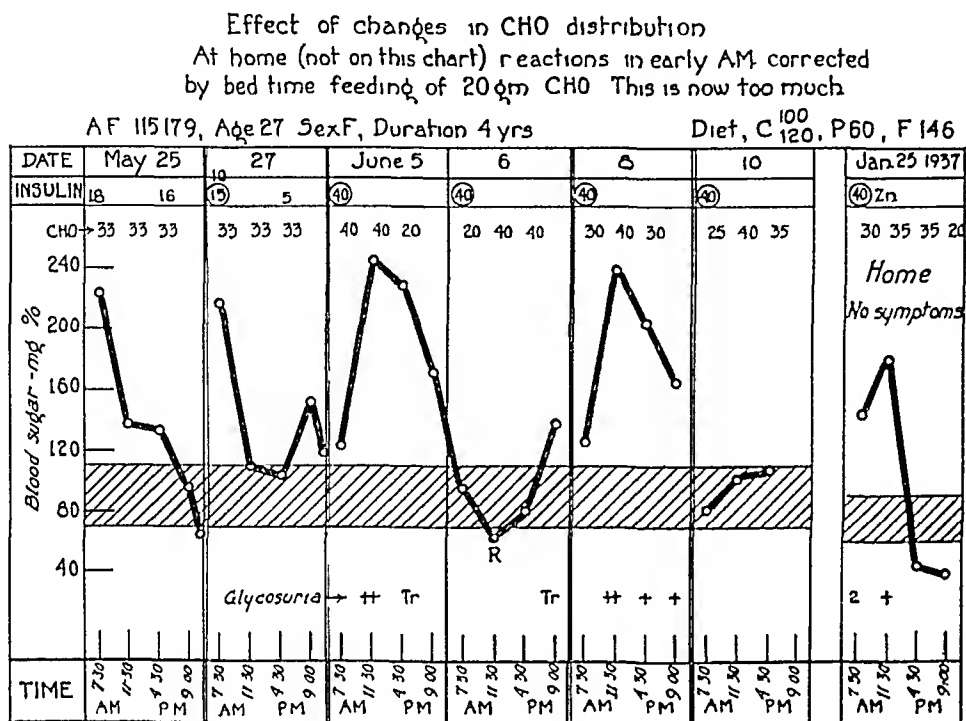


FIG 2 Though well controlled when discharged from the hospital (June 10), increased activity at home led to early morning hypoglycemia which necessitated a bed time meal The distribution of carbohydrate (30-35-35-20) which gave an unsatisfactory curve on Jan 25 has now been changed to 25-40-40-15 with good results The letter R in this chart and succeeding ones indicates insulin reaction Note symptomless hypoglycemia on Jan 25

hydrate should be obtained by deducting small amounts from the meals at the times indicated rather than by adding it to the total daily allowance, the latter procedure is apt to result in an increase in the total insulin requirement If, on the other hand, post-prandial hyperglycemia does not occur on the given dose, the carbohydrate taken on retiring may be added to the total daily allotment with only slight, if any, change in the dose of protamine About two-thirds of the patients in this series have required a bed-time meal

The case of H G (figure 3) illustrates some of these points The total diet of carbohydrate 150 grams, protein 75 grams and fat 120 grams was maintained throughout On Jan 19, with the carbohydrate distributed 50-50-50, 35 units of protamine insulin, following the 10 units of regular insulin given the evening before, proved to be too much The dose was accordingly dropped to 25 units, and since the highest blood sugar on the nineteenth had occurred before lunch, the carbohydrate

was divided 30-60-60 It is apparent from the blood sugar curve of January 21 that now the breakfast was too small and the lunch and supper were too large Therefore the diet was rearranged by adding 10 grams of carbohydrate to breakfast and subtracting 20 grams from lunch and 10 grams from supper, the extra 20 grams thus

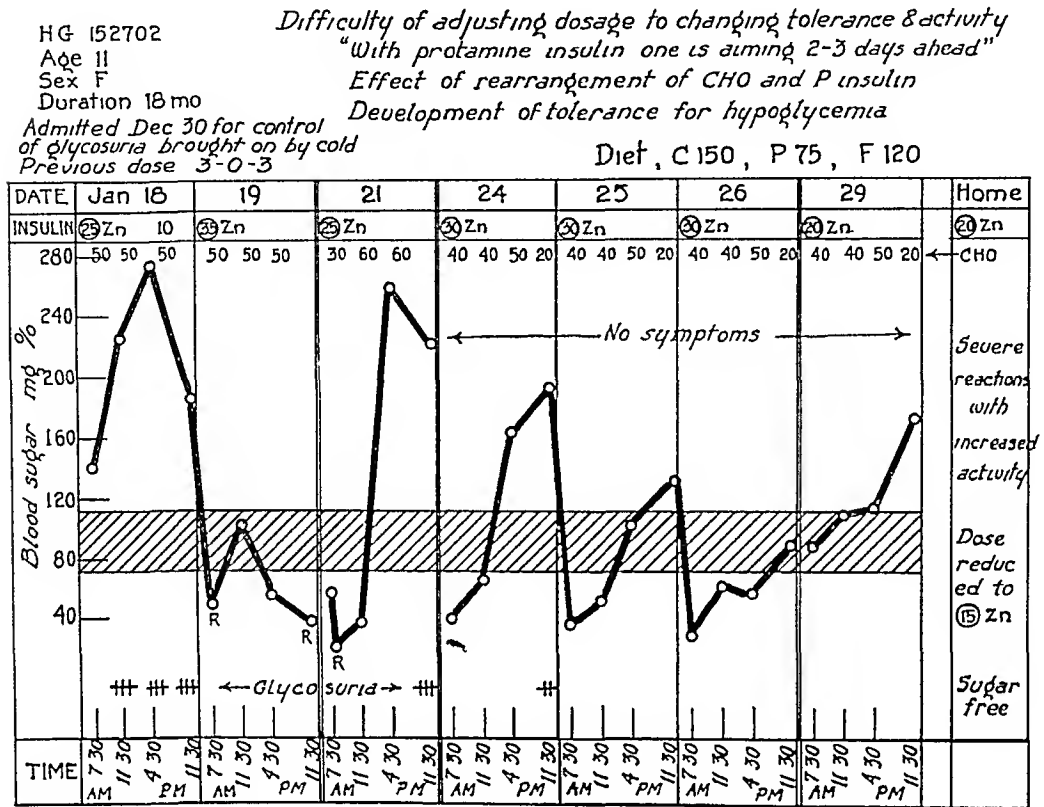


FIG 3 This patient was transferred to protamine insulin at the time when her tolerance for carbohydrate was improving after recovery from a cold This procedure under such circumstances is often attended by difficulty It was a mistake to attempt to control afternoon and evening hyperglycemia by raising the dose of protamine insulin on Jan 19 and 24 because the dose of the preceding day in each case had already produced hypoglycemia before breakfast Note progressive improvement in blood sugar curves from Jan 24 to 26 despite no change in carbohydrate distribution or dosage For further discussion see text

obtained being given at bed-time The resulting proportion of 40-40-50-20 was found satisfactory except for the persistence of early morning hypoglycemia This was due to the erroneous increase in the dose of protamine from 25 to 30 units between January 21 and 24 in a mistaken effort so to control the day-time hyperglycemia exhibited on the former date When the dose was reduced to 20 units hypoglycemia was eliminated (January 29)

It may be stated here that the distribution of protein and fat between the various meals is unimportant Also, in common with Campbell³ we have found the lower carbohydrate diets more satisfactory than those of higher value

4 The blood sugar throughout the day, including that before breakfast, may be maintained on too high a level In this relatively happy circumstance the dose of protamine insulin must clearly be increased

5 Only rarely have we observed hyperglycemia before breakfast with hypoglycemia later in the day. In the case of A F (figure 2) the curve obtained on January 24 led to a subsequent change in carbohydrate distribution from 30-35-35-20 to 25-40-40-15, the dose of protamine insulin being left the same.

6 In certain cases, with an amount of protamine insulin which gives a normal blood sugar before breakfast, glycosuria during the remainder of the day may be poorly controlled despite every effort properly to readjust the dietary carbohydrate. This situation usually requires a small dose (5 to 15 units) of regular insulin given at the same time as the protamine. In our experience with this group of patients to date, the administration of supplementary unmodified insulin before breakfast, provided carbohydrate was properly distributed, has been sufficient to take care of hyperglycemia in the afternoon as well as that occurring before lunch.

The case of J L, a severe diabetic, is illustrative (figure 4). The blood sugar curve obtained on January 21 in the out-patient department shows that a dose of protamine insulin (50 units) sufficient to give reasonable control through the day,

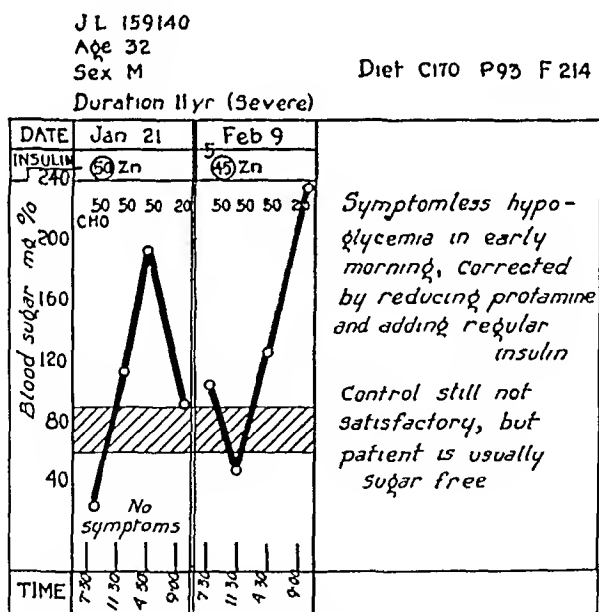


FIG 4 Effect of a small dose of supplementary regular insulin substituted for an equal amount of protamine insulin

produced marked hypoglycemia in the early morning. Reduction of the dose to 45 units corrected the hypoglycemia but resulted in heavy glycosuria after meals. The curve of February 9, with 45 units of protamine and 5 units of regular insulin, is more, though not completely, satisfactory.

The case of T L, also a severe diabetic (figure 5) is similar. Here 7 units of regular insulin were added to the amount of protamine. This, while producing hypoglycemia before lunch, permitted hyperglycemia in the afternoon. The amounts of

protamine and regular insulin, therefore, were continued unchanged, and adequate control was established by changing the proportion of carbohydrate from 25-55-35-20 to 35-45-35-20

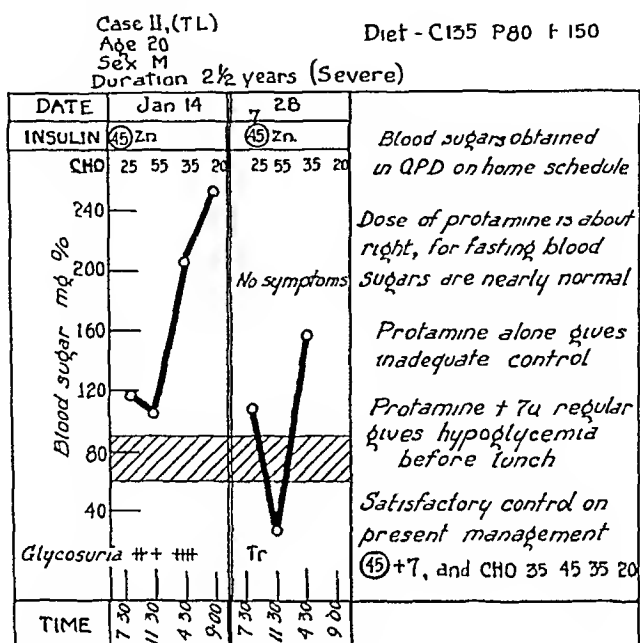


FIG 5 Effect of supplementary regular insulin added to the amount of protamine insulin

(c) Since protamine-zinc-insulin has been available it has not been necessary in any case of this series to use the method originally described by Hagedorn of giving regular insulin in the morning and the slowly acting insulin at night

ASYMPTOMATIC HYPOGLYCEMIA

It has been noted by nearly all workers that, probably due to the slowness with which the blood sugar falls, the hypoglycemia caused by protamine insulin is insidious in onset, symptoms may be slight and the level of blood sugar at which symptoms do occur is lower than when regular insulin is used. These facts find confirmation in the cases here reported (figures 1, 2, 3, 4, 5, 6). They may account in part for the common observation that reactions are fewer with protamine than with regular insulin, though it must be admitted that reactions are less frequent also because the blood sugar is better controlled.

We would especially call attention to that group of patients who, though discharged from the hospital well controlled, were found to have abnormally low blood sugars with no subjective manifestations when they were recalled to the out-patient department for analyses of the blood made under what roughly approximated home or routine conditions (figures 1, 2, 4, 5). It should be pointed out that the method for blood sugar* used in the out-

* Analyses are done on unclaked blood filtrates⁵ by the Somogyi modification¹⁷ of the Shaffer-Hartmann method¹⁶

patient department gives values for normal (60 to 90 milligrams per 100 c c) which are somewhat below those obtained by the customary Folin-Wu procedure. Nevertheless, the levels at which some of these blood sugars were found are disconcertingly low. The patient J L (figure 4), for example, walked into the clinic one morning feeling perfectly well with a blood sugar of 26 milligrams per 100 c c. While the effect of prolonged, sub-clinical hypoglycemia in the human is not known with certainty, there exists the distinct possibility that functional derangement or even structural damage to tissues may result.¹⁹ Wilder states that he is informed of one death following the use of protamine insulin. When a patient is discharged from the hospital using regular insulin, the increased tolerance for carbohydrate incident to resumption of normal activity causes but little concern with regard to the possible development of hypoglycemia, for the appearance of symptoms is a reliable guide to dosage. With protamine insulin, however, the patient is often deprived of a valuable warning signal, and the only indication of danger may be a laboratory report. It is therefore important that patients who have been sent home taking protamine insulin be requested to return to the office or clinic on two or three occasions when the urine is known to be sugar free for analysis of the blood for dextrose. Since hypoglycemia is most apt to occur in the early morning, this precaution is especially to be observed when the urine specimen passed on arising does not reduce copper.

Others^{18, 19} have directed attention to the difference in symptomatology between reactions due to regular insulin and those due to the protamine compound. Wilder has pointed out that in the case of the latter, the relative lack of perspiration, tremor and palpitation, and the common presence of headache, drowsiness, weakness and sometimes nausea and vomiting may give the impression of acidosis rather than hypoglycemia. The patient must be warned of these differences and instructed to test the urine when in doubt. Paresthesia is a common manifestation. Another peculiarity is that patients who are in unrecognized hypoglycemia may suddenly be precipitated into unconsciousness by a little unusual exertion. The tendency of symptoms to recur after being relieved by carbohydrate has been remarked by a number of observers^{3, 9, 13, 14, 18}

DIFFICULTIES DUE TO DELAY IN APPEARANCE OF FULL EFFECT

Sprague and his colleagues¹⁸ have said of the unmodified protamine insulin, "When using insulin-P, one is aiming about 72 hours ahead." This axiom is even more applicable to protamine-zinc-insulin and is well illustrated by the case of H G (figure 3, Jan 24, 25, 26), in which the blood sugar curve showed progressive improvement over three successive days with no change in the amount of insulin or distribution of carbohydrate, though it was maintained, to be sure, on too low a level. The logical deduction is that changes in dosage should not be too frequent or pronounced.

For the physician schooled in the use of ordinary insulin this is not an easy lesson to learn. The temptation to increase the dose of protamine insulin daily when the patient is excreting sugar is difficult to resist. The lapse of 48 or 72 hours, however, may show that an alteration contemplated earlier would have been not only unnecessary but confusing. It is our belief that many unsatisfactory results, including some of our own, are due to failure to recognize this truth.

The slow and prolonged action of protamine insulin has several disadvantages.

(a) It lengthens the period of stabilization in severe cases. This means additional expense. We have rarely found it possible to reach a satisfactory adjustment with hospitalized patients short of 10 to 14 days, and with outpatients a longer time, with frequent visits, is required.

(b) It renders difficult the transfer to protamine insulin of patients whose tolerance for carbohydrate is rapidly improving, such as those recovering from acidosis, infections and surgical operations.

The patient C. G. (figure 6) for example had been brought out of acidosis and maintained with regular insulin for 10 days after his admission in pre-coma. About the eleventh day (January 8) his tolerance began to improve and the dose of 90 units of regular insulin proved excessive. On January 9, when treatment with protamine insulin was begun, the total dose was accordingly reduced to 80 units (70 of protamine and 10 of regular insulin). This, while apparently satisfactory for the day in question, led to reactions the next, and for the following three days, despite daily reductions in dosage, the patient was in severe, almost constant hypoglycemia due to our inability to estimate the speed at which his insulin requirement was decreasing. Finally no insulin of any kind was given after the injection of 35 units of protamine on the morning of January 12, and not until January 14 did the blood sugar rise appreciably above the normal. On January 15 treatment was resumed with smaller amounts of protamine insulin.

It is probable that in this case the exclusive use of regular insulin, with its relatively short latent period and duration of action, until complete stabilization had been reached would have yielded better results than those obtained by the more prolonged and inflexible action of protamine. On the basis of similar cases we are now reluctant to transfer a patient to the new insulin until a definite plateau of tolerance has been attained with ordinary insulin. Again, it is important to recognize that, with patients who require more than 20 or 30 units daily, this means either extended hospital care over a single period of time or rehospitalization for the express purpose of making the transfer after tolerance has become established under management at home.

Ioslin¹ has stated that the regulation of a previously untreated diabetic with protamine insulin is a much simpler matter. Our experience with this procedure has been limited but encouraging.

(c) Protamine insulin theoretically is disadvantageous in diabetic emergencies such as coma, infection, childbirth and operations. In all these the

condition of the patient is subject to rapid fluctuations against which a quickly acting, easily variable insulin would seem to be the weapon of choice. Exceptions to this view would be emergencies arising in patients already under treatment with protamine insulin. In such cases, as suggested by Colwell⁴ and implied in the report of Kepley, Ingham and Crisler,¹⁰ it may be wise to continue the basic dose of protamine insulin, supplementing it by regular insulin. The employment of the two kinds of insulin in cases of acidosis in which the protamine compound has not previously been used has been reported favorably in a few instances,^{10, 19} but the question of whether this unnecessarily complicates treatment cannot be answered finally without further experience.

(d) The prolonged effect of protamine insulin may, under certain circumstances, involve difficulty of yet another sort. If once a day's supply has been injected under the skin, a sudden illness should prevent the taking or retaining of food, serious hypoglycemia would be likely to ensue unless dextrose were administered parenterally at intervals for 24 hours or longer. One case of this kind has been brought to our attention.

ALLERGY

Three patients in this series developed red, raised, itching lesions at the sites of injection a few days after starting treatment with protamine insulin. One of these had taken ordinary insulin irregularly at home without urticarial reactions. The other two had never received insulin of any sort. In each case the local allergy disappeared spontaneously within a week or two despite continuance of the injections. Joslin⁹ mentions two similar cases not observed by him.

GENERAL PRINCIPLES GOVERNING THE USE OF PROTAMINE INSULIN

Although the treatment of patients with protamine insulin is a highly individual matter, the combined experience of a number of investigators permits the establishment of certain general principles which at least for the present should govern its use. These can best be discussed as applying to two classes of patients.

I *Patients Who Should Begin the Use of Protamine Insulin Only in the Hospital*. This class includes all children, and those adults whose disease is severe or complicated, who are unstable and who live so far from a laboratory that determinations of the blood sugar are not feasible. These patients fall into two groups.

(a) Those who have not received insulin of any sort. Such patients may be treated either by (1) starting the administration of protamine insulin at once, with or without supplementary doses of regular insulin, or by (2) stabilizing the patient entirely with regular insulin and then transferring to protamine insulin.

Although in a few cases reported by other writers^{10, 11} coma has been treated with protamine insulin alone, it would seem safer for the time being to manage all previously untreated cases with severe acidosis, infection or surgical complications by means of regular insulin only. The transfer to protamine insulin should be made as outlined in (b) below and only after a definite plateau of tolerance has been reached.

The other patients in this group may be given protamine insulin uninterruptedly from the time of admission. The dietary carbohydrate should as a rule be apportioned $\frac{1}{5}$ for breakfast, $\frac{2}{5}$ for lunch and $\frac{2}{5}$ for supper. A single injection of protamine insulin, the amount determined by an "educated guess," is given each morning an hour before breakfast, supplemented if necessary by a smaller dose of regular insulin at the same time. Although some authors⁸ have found it permissible to give the two kinds of insulin simultaneously in the same syringe, the majority agree that this procedure leads to the precipitation of a certain and probably variable portion of the regular insulin by the protamine present and tends to yield inconstant results. The same syringe may be used provided that the regular insulin be withdrawn and injected first, but the sites of injection should be separate. Specimens of the urine and, if possible, the blood, are obtained on arising and three hours after each meal and examined for sugar. Unless grossly inadequate the dose of protamine insulin should not be changed before three or four days or more have elapsed. As improvement occurs the regular insulin may be reduced and finally omitted, although in some cases its permanent use is necessary. Further rearrangement of carbohydrate should be made as indicated. The safest and best guide to the proper amount of protamine insulin is the level of the blood sugar in the early morning. In order to allow for the effect of increased activity at home, it is a wise precaution to discharge hospital patients with a dose which permits slight hyperglycemia.

(b) Those who are already receiving regular insulin. In these cases it is usually best to begin with an amount of protamine equal to the total daily requirement of regular insulin. For the first few days, at least, glycosuria is better controlled by giving simultaneously but in a different site a dose of regular insulin equal to from one-third to one-fourth of this amount. The regular insulin may be in addition to the protamine used, or may be substituted for an equal quantity of the latter, depending on the case. In most instances it is possible to decrease the dose of regular insulin a few units at a time over a period of three or four days until finally protamine insulin alone is given.

II *Patients Who Can Safely Begin the Use of Protamine Insulin in the Office or Out-Patient Department*. These patients are adults whose disease is uncomplicated and of only moderate severity, who give promise of being fairly stable and who live within convenient distance from a laboratory. They also fall into two groups.

(a) Those who have not received insulin of any sort Joslin^{7,8} emphasizes the safety, simplicity and wide applicability of using only protamine insulin in such cases. A patient of this type, *provided he shows no ketosis*, should be given a diet, weighed if possible, with the carbohydrate divided $\frac{1}{5}$ for breakfast, $\frac{2}{5}$ for lunch and $\frac{2}{5}$ for supper, and should be taught the technic of urinalysis, tests being made on arising and about three hours after each meal. Having been instructed in the method of administration, he should be told to take one hour before breakfast a dose about one-third less than that which, on the basis of experience, the physician thinks may be his requirement. This dose should not be changed for the next three or four days, the patient meanwhile testing the urine as described and communicating the results to his doctor daily. It is far better to start with a relatively small dose of protamine insulin and permit glycosuria for a few days than to begin with too large a dose which may, in 48 or 72 hours, produce hypoglycemia in the early morning. The dose can be increased more easily than it can be reduced. Subsequent changes in dosage should not be made daily. When the urine tends to become sugar free, and particularly if the specimen on arising is clear, a determination of the fasting blood sugar should be made, or if this is impossible the dose should be reduced a few units every three or four days until sugar reappears in the urine, then raised a notch. If hypoglycemia does develop, the dose should be promptly dropped to a level calculated to result in glycosuria and again be built up gradually. By this time further adjustments in carbohydrate distribution as described earlier may be necessary, including possibly a bed-time feeding. If any unusual difficulties are encountered the patient should be hospitalized.

(b) Those who are already receiving small or moderate amounts of regular insulin. It is our belief that in this group only the patients who are comparatively stable and who require not more than 20 or at the most 30 units daily should be transferred to protamine insulin outside the hospital.* Since the supervision of ambulatory patients cannot be so close as that of hospital patients, the initial dose of protamine insulin should be equal to only about two-thirds of the previous total daily requirement, the other third, more or less, being given as regular insulin. The next day half the amount of regular insulin, or possibly none at all, depending on the urine tests, may be given. Further adjustment of diet and insulin may be made as outlined in the preceding paragraphs.

Because the hypoglycemia produced by protamine insulin is so commonly asymptomatic, the importance of making frequent determinations of the blood sugar, both during the period of adjustment and after the patient has gone home, cannot be overemphasized.

* Richardson and Bowie¹⁴ using unmodified protamine insulin, have reported the out-patient transfer of over 30 patients whose requirements were less than 40 units daily.

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SOME OF THE PRACTICAL PROBLEMS IN THE SERUM THERAPY OF BACTERIAL INFECTIONS

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SERUM therapy is an outgrowth of the discovery that microorganisms, the bacteria, are incitants of infectious disease. As such, it is difficult to differentiate the results of the branch from those of the parent stem. For example, in diphtheria, early diagnosis with prompt isolation has alone had a far-reaching effect not only upon the morbidity but also, indirectly, upon the severity of the disease, and it is difficult to distinguish the effect of the discovery of the diphtheria bacillus and of improved public health methods from that of the specific treatment with antitoxin, on the morbidity and mortality of the disease. Much of the decline is to be attributed to advancing medical science, apart from specific serum therapy, as exemplified in the diminishing morbidity and mortality of other infectious diseases. Much of the lowered mortality of diphtheria, however, may be accredited to treatment with antitoxin, and these results have reached an astounding magnitude when measured in terms of human happiness and welfare.

Forty years' experience with diphtheria antitoxin illustrates very strikingly the major problems of serum therapy. In some respects they may vary according to the disease and its bacterial incitant, in others, they do not differ materially. These problems may be classified under two main headings: one, the preparation of potent, effective sera in the laboratory, the other, early treatment with adequate dosage at the bedside. Preparation of diphtheria antitoxin has advanced steadily. There has been marked improvement as evidenced by a more than tenfold reduction in dosage and an even greater increase in potency. No one now criticizes the quality or questions the potency of the diphtheria antitoxins that are distributed under governmental supervision and control. Corresponding reduction in mortality at first paralleled the improvement in antitoxin, but there is now a residual mortality that eludes even this specific therapy. The residual mortality in diphtheria is now to be attributed to delayed treatment or inadequate dosage, possibly entirely to delayed treatment. It would be important from a public health standpoint to have complete information regarding every fatal case of diphtheria.

Effective serum therapy depends primarily upon the neutralization of toxic substances, secondarily, upon the destruction of the bacterial incitant.

* Received for publication July 15, 1937.

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The extent to which one process is dependent upon the other, as well as the precise sequence of events in the different infectious diseases, offers a most important field for investigation. Unfolding knowledge of group and type specificity reveals the subtle interrelationships of the antitoxic and antibacterial activities of serum in relation to the protective mechanism of the tissues of the host that underlie effective serum therapy.

The antitoxic action of serum therapy has been contrasted very sharply with the antibacterial phenomena attributed to the sera that are used in the specific treatment of infectious diseases, the bacterial incitants of which invade the tissues generally. So sharply have these two activities been differentiated that the antitoxic action of the antibacterial sera has been overshadowed. In the laboratory, studying the different activities or manifestations of immune sera, it is important to classify and differentiate sharply, but when one turns to the study of effective serum therapy in the infectious processes of the tissues, it is not only difficult but unwise to differentiate these activities.

Sera differ in their antitoxic and in their antibacterial action, but just how they differ and to what extent, or how they are interdependent and to what extent, is of paramount concern to us all since these relationships underlie all phases of vaccine and serum therapy. The type specificity of botulinus antitoxin on the one hand, and on the other, the type specificity of the anti-pneumococcus sera represent extremes.

Antitoxic serum exerts an antibacterial effect, possibly directly, but more obviously indirectly upon the incitant of infection in the tissues. The diphtheria, tetanus, and botulinus antitoxins are the most representative. With diphtheria and tetanus infections, group and type specificity are not involved, despite the fact that strains of these microorganisms vary widely in their toxigenicity and antigenicity, not that the diphtheria bacillus may not be divided into subgroups on the basis of selected characters, but that the toxin produced by the different strains has invariably been neutralized by the standard antitoxin. In diphtheria, the administration of antitoxin neutralizes the toxin and crisis occurs promptly. Following this, the diphtheria bacilli are destroyed by the protective mechanism of the tissues unless these bacilli are so situated that they evade the action of the tissues and survive as relatively harmless parasites in the carrier state. However, when the disease has progressed to a later stage, the tissues are vitally injured. Neutralization of the free toxin by antitoxin is inadequate and the protective mechanism fails to destroy the diphtheria bacilli. These examples of the simplest form of serum therapy very strikingly illustrate its fundamental limitations. Tetanus antitoxin acts similarly. The tetanus bacillus, however, is less readily established as a parasite in the tissues when its toxic activity ceases to injure the tissues. Recovery, when it occurs, is complete in that the incitant does not persist as a parasite in the tissues. Although group or type specificity does not figure in serum therapy of tetanus or diphtheria infections, the toxigenicity and antigenicity of different strains

of these microorganisms are most important factors in the production of potent antitoxins

With the incitants of botulism, which is also a simple toxemia without invasion of the tissues by the incitant, type specificity plays an important rôle in serum therapy because the neutralization of the toxins in the test tube as well as in the tissues depends upon the homologous relation between the incitant and the antitoxin that is used in serum therapy. Thus, the antitoxin of A, of B, and of C microorganisms is effective only in the corresponding infections of A, of B, and of C types. The limitations of serum therapy, as illustrated by the above cited examples of diphtheria infection, are even more sharply defined in botulism. To be effective, an antitoxin must be administered almost immediately. The crisis of the disease process, irrespective of serum therapy, occurs promptly because the disease is so largely a toxemia and practically uncomplicated by even a localized infectious process. In fact, the majority of the cases are simply the absorption of a large amount of toxin. The crisis occurs so promptly that the patient either dies or recovers irrespective of the administration of serum. Nevertheless, the antitoxin should be given because, after all, it is impossible to determine by any clinical signs whether the crisis has been reached or passed.

An antitoxic serum exerts an antibacterial effect when it is used in the treatment of an infectious process the incitant of which is localized, and the disease largely, if not entirely, toxemic in character. Moreover, antibacterial sera exert an antitoxic effect either directly or indirectly upon the incitant of the more generalized infectious diseases. The antipneumococcus and antimeningococcus sera are representative examples of antibacterial sera. Antipneumococcus serum exerts definitely specific action, sharply defined according to the type specificity which is related to the carbohydrates of the microorganisms. The direct antibacterial action is well recognized and is evident in the protection test in mice and the effect of the serum on phagocytosis.

In the absence of demonstrable toxin, it is difficult to obtain evidence of an indirect antibacterial action associated with an antitoxic activity that conserves the tissues and favors the destruction of the pneumococci by the protective mechanism that follows neutralization of the toxin. However, the antitoxic action is manifested by the critical effect of the serum on the febrile reaction of pneumonia corresponding to the crisis that occurs spontaneously. The neutralization of the toxin may precede or follow the destruction or inhibition of the pneumococci in the tissues. However, following neutralization of its toxic activity, the pneumococcus may persist as a parasite relatively harmless to its host, as evidenced by survival of the pneumococcus after the crisis of pneumonia, and in the highly immunized animal when it becomes attenuated and its toxic activity nil. The virulence of these pneumococci is lost, they are no longer toxic but continue as parasites¹. Thus it is that the antibacterial antipneumococcus serum doubtless

exerts an antitoxic as well as an antibacterial effect when it is used in the treatment of pneumonia

The antimeningococcus serum also, quite similarly, exerts a definite and specific effect. The antitoxic activity of this serum is, at present, stressed. As in pneumonia, there has always been clinical evidence that the serum exerted a marked antitoxic as well as antibacterial effect. On account of the general insusceptibility of laboratory animals to infection, it has been and is difficult to differentiate the antitoxic and antibacterial action of antimeningococcus serum. However, results of protection tests in mice²⁻⁵ with cultures suspended in mucin do distinguish different degrees of activity in different sera. The intracutaneous test⁶ and protection tests against lethal doses of toxic extracts or filtrates in animals⁷⁻¹³ are not yet of practical value in the titration of antitoxic potency.

Antistreptococcus sera exert definite and specific antitoxic and antibacterial effects in the treatment of infection. The specific relationship is marked and complicated with the streptococci because it relates not only to the antitoxic activities of the serum and the antigenic activity of the toxins in producing the antitoxic serum,^{14, 15} but also to the antibacterial activity of the serum as it is manifest in the protection test¹⁶⁻¹⁹. The study of antistreptococcus serum, even in its present elementary stage, has revealed the most striking and convincing demonstration of how essential are the antitoxic, as well as the antibacterial activities of the serum to an effective serum therapy of streptococcus infection as soon as it has become generalized. In the earliest stages of certain infections, the antitoxic activities^{20, 21} may suffice as they do in diphtheria. The direct antitoxic effect in neutralizing the toxin and the indirect antibacterial effect by favoring the protective mechanism of the tissues suffice to determine recovery—possibly with or even without any direct antibacterial action of the serum. In all these actions and reactions, however, the homologous relations are important on account of the marked type and toxin specificity manifested by the different hemolytic streptococci.

Although specificity of the toxins is well marked, it has no relation to the disease processes incited by the hemolytic streptococci—scarlet fever, erysipelas, puerperal fever, etc. No specific etiological relationship has as yet been established. The toxic activities of the different strains vary greatly not only in potency but in character. Similarly, the antigenic potency and valency also vary with the strain and irrespective of the toxin group, specificity, or titer of the toxins.

The antitoxic activities of the serum thus accordingly vary^{15, 22-26}. Within a group the potency of serum produced with one strain may be high and the valency narrow, whereas in that produced with another strain, the converse may obtain. Although in general the neutralization of the toxin takes place in the homologous relation according to groups, the potencies and valencies of the different antitoxic sera vary widely. Combination of representative sera may broaden the valency beyond that manifested by either

serum separately As a result of the study of more than 1500 cultures, two strains have been selected with which, in combination, it has been possible to obtain an antitoxic serum of such broad valency that the toxins of all strains encountered thus far are neutralized Finally, and what is of the utmost importance, qualities may be supplied by the tissues of the animal host, which doubtless account in large measure for the manifestations of the antitoxic as well as the antibacterial effect of heterologous sera in infectious processes whether studied clinically in the treatment of human infection or experimentally in animals

Factors which further complicate the problem of effective serum therapy with all of these bacteria are differences in the cellular susceptibilities of the microorganisms themselves as well as the activities of the tissues in their presence For example, the biologic stability and also, so to speak, the fragility of the pneumococcus cell in disease processes, together with its capacity for adaptation, are determining factors in the serum therapy of pneumonia as they are in the prognosis of the untreated disease

The thermal limits of growth, depending upon the strain and a favorable environment, vary with the pneumococci from 39°C to about 41°C ^{27, 28} In immune serum, the pneumococcus cell vegetates at 37°C At temperatures above the thermal limits of growth, varying degrees of lysis may take place Hyperthermy, experimental elevation of body temperature, may inhibit, or even eliminate temporarily, the pneumococcemia of some infections in susceptible animals, whereas it may hasten the course of others ²⁹ Treatment with immune serum induces crisis in the febrile reactions, there is neutralization of the toxemia and marked destruction of the bacteria The pneumococcus cell is fragile, and especially so if compared with the streptococcus, although the thermal limits of growth of many strains of hemolytic streptococci do not exceed materially those of some of the pneumococci ²⁷ Immune serum in streptococcus infection may induce pseudo crises in the febrile reaction without affecting to a corresponding degree the bacteremia which may, and often does, progress The streptococci, moreover, produce a toxin, and, like strains of the diphtheria bacillus, vary greatly in this respect Certainly the quantities produced by some of the streptococcus strains can scarcely be recognized experimentally, yet when these streptococci invade the tissues of a host, the febrile reaction induced is convincing proof of their toxigenic capacity The toxin of the pneumococcus, when this microorganism is cultivated *in vitro*, has not been recognized, yet the febrile reaction of pneumonia is convincing proof of the toxigenic activity of this incitant of infection The pneumococcus is toxigenic when developing in an animal host but not under ordinary experimental conditions *in vitro* Effective antibacterial sera in the treatment of pneumococcus and meningococcus infections are produced by the immunization of horses with living virulent cultures Moreover, antitoxic streptococcus sera of the highest potency, in my experience, can only be obtained with living cultures and as a

result of the development of the streptococci in the horses undergoing immunization

Evidence of wide variation in the subtle cellular susceptibilities of the bacterial incitants of infection accumulates when the toxigenic and antigenic activities are studied for the purpose of preparing therapeutic sera of high potency and broad valency. The criteria for the selection of cultures for antitoxin are sharply defined: a potent toxin of high antigenic value must be produced. The vicissitudes of maintaining, not to mention developing, diphtheria strains for antitoxin production during the past 40 years are well known. Even more convincing is recent experience with the selection of strains of the hemolytic streptococci for the preparation of therapeutic serum. The same criteria in use for the diphtheria cultures must be fulfilled, and, in addition, there must be taken into account qualitative as well as quantitative differences in the kind of toxin produced in relation to its antigenic activity.

The criteria for the selection of cultures for production of the so-called antibacterial sera are not so sharply defined, apart from the empirical test of producing potent therapeutic serum. For the pneumococci, virulence and possibly carbohydrate production are practically the only guides. For the meningococcus, until very recently, the agglutination reaction has been one of the most valuable aids because the valence and antigenicity can be determined within the limitations of the significance of this reaction³⁰⁻³². The precipitation reaction,³³⁻³⁵ the virulence test with mucin in mice,² and several tests of toxic activity^{6, 8, 36-38} are now available to demonstrate comparative differences in strains. It still remains, however, to correlate these various activities of the culture with its efficacy in the production of potent therapeutic sera. The selection of freshly isolated strains has been stressed, but these strains vary, and it is perhaps far more important to select stable representative strains of proved high antigenic potency and broad antigenic valency and, as is now practicable, to maintain their biologic status^{2, 3, 31, 32, 34, 39-41}.

An immediate practical problem concerns the value of concentration or separation of the active globulins of antitoxic and antibacterial sera. In addition to economic considerations, there is the question as to whether or not the loss which concentration entails is due entirely to the failure to recover all of the active substances or whether certain supplementary or complementary activities of the sera are eliminated. Certainly it is not conceivable that there is a gain in therapeutic value save as the result of elimination of extraneous protein which may have a deleterious action as evidenced by the greater proportion of serum reactions with the unconcentrated serum as compared with the concentrated. However this may be, the concentration of diphtheria antitoxin, for example, has become an established procedure. Moreover, physicians at the bedside will invariably administer refined preparations in preference to the untreated serum. Concentration as it relates to the preparation of the antipneumococcus, anti-

meningococcus, and antistreptococcus sera, has only recently been adopted. It has, however, become essential from a practical point of view. Experience with the concentrated as compared with the unconcentrated products is limited to a comparatively short period. Moreover, during the past decade there has been a marked improvement, as a result of experience in their preparation, in the therapeutic value of all of these sera generally available. The potency has been materially advanced and the valency broadened. The data and statistics are, therefore, not generally comparable—quite apart from the variations in the severity of the infections treated with the different sera. I therefore do not feel competent to evaluate the reports of other observers and have been forced to rely upon personal experience with the sera prepared in our laboratory during this period. Fortunately some direct comparisons are possible from the data that have been collected through the kindness of Dr. Cole of the Rockefeller Hospital and of Professor Longcope and Professor Park of Johns Hopkins Hospital, who have had opportunities of comparing the unconcentrated and the concentrated sera prepared by identical methods and of equivalent potencies and valencies. These data I consider reliable.

During the short period that the sera have been refined by special methods,⁴²⁻⁴⁴ 25 cases of type-I pneumonia have been reported by Dr. Abernethy from the Rockefeller Hospital⁴⁵, three more may now be added to this series in which no fatalities have occurred. In an earlier series of 371 cases treated with unconcentrated serum, Cole reported a mortality of 10.5 per cent.⁴⁶ The results in these two series, however, are not strictly comparable. In those cases treated with the concentrated serum the Neufeld technic was available. The prompt type diagnosis thus provided accounts for an earlier administration of serum, and under these improved conditions of treatment a lower mortality may well follow. In 89 cases of meningococcus meningitis treated at Johns Hopkins Hospital with the concentrated product alone, there were 8 deaths (8.9 per cent). In 31 cases which were given both concentrated and unconcentrated serum, there were 3 fatalities (9.7 per cent). During the same period, 32 patients were treated with the unconcentrated serum with 4 deaths (12.5 per cent). In each group the fatal cases included some which had complications of pneumonia or which were moribund when admitted, but survived the first treatment longer than twenty-four hours. Dr. Tillett reported on a group from this series in 1935.⁴⁷ These results cannot be credited wholly to the serum that was used because they may be due quite as much, or even entirely, to early treatment with adequate dosage. Serum reactions were materially diminished with the concentrated preparations. Some reactions, however, have been noted with the concentrated antimeningococcus serum when given intraspinally, although the percentage of protein does not materially exceed that of the untreated serum.

Problems of serum therapy thus relate to the preparation of the serum on the one hand and, on the other, to its administration. The selection of

strains according to their toxigenicity, antigenicity, and valency is of first importance in the preparation of the antibacterial serum as it is with the antitoxic sera, and especially is this true when type specificity is involved. The quality and potency of the diphtheria antitoxins are now no longer questioned. There has been steady improvement in the antibacterial sera during the past ten years. It has been possible to select representative strains of the meningococci, the antigenic potency and valency of which make it possible to prepare effective polyvalent antimeningococcus serum. The antigenic properties of these strains can be maintained in the laboratory so that it is unnecessary to resort to freshly isolated strains, save as a means of replenishing or improving standards.

In the preparation of antipneumococcus serum, the type specificity of the strains as antigens is so marked that it has not been possible to prepare effective polyvalent serum. Early type diagnosis and the administration of the homologous serum are therefore essential.

In the preparation of antistreptococcus serum, not only must the type and toxin specificity of the strains be considered, but also the antigenic action, which varies. A serum of broad valence is essential since early type diagnosis is not practicable as in pneumonia. In the production of antitoxic serum it is now possible by the selection of two strains of hemolytic streptococci to obtain a serum of high potency and a valency so broad that it includes the toxins of practically all strains.

Preparation of all these sera has advanced to the point where it is now necessary to stress particularly the other side of the problem—namely, early diagnosis and early treatment with adequate dosage.

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THE COMPARATIVE VALUE AND THE LIMITA- TIONS OF THE TREPHINE AND PUNC- TURE METHODS FOR BIOPSY OF THE STERNAL BONE MARROW

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THE last few years have witnessed a striking development of interest in the sternal bone-marrow biopsy. This is undoubtedly due to at least two factors: the rapidly increasing interest in hematology which followed the discovery of the value of liver in pernicious anemia, and the increasing recognition that the so-called "blood diseases" are in reality disorders of the blood-forming organs, more particularly of the bone-marrow. Biopsy of the sternal marrow, introduced by Seyfarth¹ in 1923, rapidly displaced the much more difficult biopsy of the tibia which was practised by Zadek,² Peabody,³ and a few others. The diagnostic value of the sternal bone-marrow biopsy particularly in cases presenting anemia, leukopenia, and thrombocytopenia has already been referred to in another paper.⁴ The technic of the procedure consists in brief of the removal by trephine of a small plug of bone from the sternum. Two types of preparations are obtained: (1) *sections*, made by imbedding and cutting the small plug of bone removed, and (2) *smears*, made by touching gently bits of bone removed by curette from the trephine cavity. In the above paper and in another describing the appearance of the bone-marrow at biopsy in pernicious anemia,⁵ the important features of both types of preparation were stressed, i.e. from the sections are obtained general ideas of the cellularity of the marrow, the topographical relations of various groups of cells, and the presence or absence of islands of embryonic cells. From the smears, careful study of the individual cells can be made, the cells appearing much as in a blood smear without the distortion and shrinkage frequently found in the sections. The definite impression has been obtained that in order to make a proper study of the sternal bone-marrow at biopsy, both the marrow sections and smears are essential, each type of preparation having its definite shortcomings and advantages.

* Read before the American Medical Association, Section on Pathology and Physiology, June 9, 1937. From the Medical Service and Hematology Laboratory, Beth Israel Hospital, Boston. Written in honor of the Festschrift of Dr. Joseph H. Pratt who has been keenly interested in the development of the bone-marrow biopsy and whose encouragement made some of the early studies possible.

Aided by a grant from the Charlton Fund, Tufts College Medical School.

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More recently another method for examining the sternal marrow has been introduced. In this method, a modified lumbar puncture needle is plunged into the sternal cavity and material obtained for smears by suctioning with a syringe. First introduced by Arinkin⁶ and other Russian investigators, the method became widely practised, so much so that within the last few years two monographs (Segerdahl,⁷ Nordenson⁸) have appeared based entirely on this procedure. A large number of articles extolling the ease of technic and the diagnostic value of the method have appeared.⁹ As far as we know, there has been no critical appraisal of this method nor any comparison of the results with those obtained by the trephine method. The present paper, which deals with a critical examination of these questions, is based upon a comparison of the data obtained by both methods in 20 consecutive cases, together with a review of the pertinent data from about 200 previous biopsies.

METHODS

Under aseptic precautions and following thorough infiltration of the skin and periosteum with novocaine, a small incision 1 to 2 cm in length was made over the midsternum in the region of the fourth intercostal space. The periosteum was exposed, incised, and retracted in the ordinary manner. A puncture diagonally through the anterior lamella of the sternum was then made with a lumbar puncture needle which had been shortened to about one-half its regular size. When a sensation of "give" was obtained, the stylet was removed, and a very small quantity of material aspirated into a 20 c.c. syringe. Ordinarily, less than 0.5 c.c. of material was removed and this was spread gently on glass slides as with blood smears. Following this puncture, a small trephine was introduced into the sternum and a small plug of bone removed. This was immediately placed in Zenker's solution containing 5 per cent of glacial acetic acid sufficient for decalcification. The cavity resulting from the removal of the plug of bone was carefully scraped with a fine curette, bits of bone being removed which were then gently smeared on glass slides. Reticulocyte preparations were made with both the puncture and trephine preparations by using slides which had previously been coated with a thin film of cresyl blue (0.3 per cent brilliant cresyl blue in 95 per cent alcohol). Both types of smears were stained either with Wright's stain or with Giemsa stain and in several instances a combination of both stains was used. The Wright's stained preparations gave uniform results and presented delicate cellular pictures. The Giemsa stained preparations were more "brilliant" and showed better staining of the granules, although the nuclei were at times overstained. Differential counts of the "puncture" and the "trephine" smears were made, in both cases at least 500 cells being counted. Reticulocyte counts were made in most instances, 1000 non-nucleated erythrocytes being counted. The sections, after ap-

propriate fixation, were prepared in the ordinary way with paraffin and stained with eosin-methylene blue *

STERNAL BONE MARROW BIOPSY
Trepine vs Puncture Method

	Trepine	Puncture
1 The Smears—General Exam	Normally highly cellular	Frequently very few marrow cells
2 Ratio Nucleated R B C to W B C	About 1 : 1	Usually about 0.5 : 1
3 Types of Nucleated R B C	All types, including most primitive, present	Primitive cells much diminished, often absent
4 Reticulocytes	5-15%	0.5-2%
5 W B C	Essentially similar findings	_____
6 Megakaryocytes	Common	Infrequent
7 Ease of Performance	Relatively difficult	Easy—Amassing of data Serial observations Children
8 Interpretation	Relatively easy, because both sections and smears obtained	Smears only, often with more blood than marrow, make interpretation difficult

The morphological characteristics of the various cells encountered in the marrow have already been described in previous papers. All cells were carefully studied from the standpoints of size, shape, cytoplasmic characteristics (amount, color, granules, vacuoles) and nuclear characteristics (size relative to cell, type of nuclear chromatin, nucleoli). The leukocytic cells discriminated were the histiocyte (hemohistioblast), myeloblast, promyelocyte, myelocyte, metamyelocyte, mature polymorphonuclear cell, eosinophile and basophile. Our nomenclature for the erythroblastic cells is based on previous studies in pernicious anemia and differs somewhat from that of other authors. The most primitive cell of this series is the erythrogone, which is found in all conditions in which the marrow is hyperplastic and is apparently the forerunner of both the megaloblast and the normoblast. In the absence of "liver extract substance" (pernicious anemia and related states), an abnormal or megaloblastic type of erythropoiesis takes place. Various grades of maturity of megaloblasts are seen and these may be arbitrarily classified as "A," "B," and "C."

When "liver substance" is present, normal red blood cells are formed, i.e. *normoblasts*. Similarly, three types of normoblasts are distinguished "A," "B," and "C," corresponding to the terms frequently used in the literature of macroblast, erythroblast, and normoblast respectively.

RESULTS

A The Smears Differential counts from both types of preparations in 20 cases together with the ratio of nucleated red blood cells to white blood

* Best results in staining both smears and sections were obtained by using the Gruebler stains

TABLE I
Biopsy Smears

		Normoblasts		W B C								Retic	RBC	WBC	
		Eg	Meg	"A"	"B"	"C"	P	P 2 and 3	My- elo- cytes	Blasts	His- tio- cytes				L
1	Anthony P (a)* (b)†	42 04		131 02	264 12	150 399	96 128	182 357	107 69	07 04	03 02		18 23	72 26	1 138
2	Margaret B (a) (b)	64 52	188 140	26 06	98 92	96 80	70 128	198 226	114 140	06 18	10 —	116 88	10 24		1 11 1 17
3	Maria S (a) (b)	72 02	96 02	30	99 56	168 154	81 106	192 260	111 54	— —	— —	141 360	09 06	167 75	1 115 1 37
4	Catherine D (a) (b)	— —	— —	30 04	128 58	142 220	60 68	342 420	184 170	60 04	32 —	24 54	24 22	96 14	1 23 1 25
5	Margaret S (a) (b)	67 12	192 26	— 28	10 138	25 82	70 80	217 276	192 262	45 38	15 06	125 32	47 20	92 57	1 24 1 25
6	Catherine S (a) (b)	11	—	42 48	99 158	150 70	98 97	256 237	115 97	48 02	— 02	170 214	69 74		1 25 1 26
7	Frank C (a) (b) (Poor in cells)	02 —	—	48 15	218 65	100 45	66 175	256 445	186 125	10 —	04 —	76 120	34 05	52 19	1 17 1 68
8	John F (a) (b)	— 08	—	04 38	190 122	156 88	44 68	276 310	212 146	34 32	12 16	54 138	18 34	47 08	1 17 1 31
9	Swan A (a) (b)	90 25	306 130	16 27	98 101	58 156	98	100 252	94 94	16 16	02 02	30 174	92 18	54 187	1 87 1 13
10	Christine Y (a) (b) (Poor in cells)			52 14	234 92	108 67	62 194	206 306	174 127	30 11	10 03	98 172	26 14	37 11	1 13 1 4

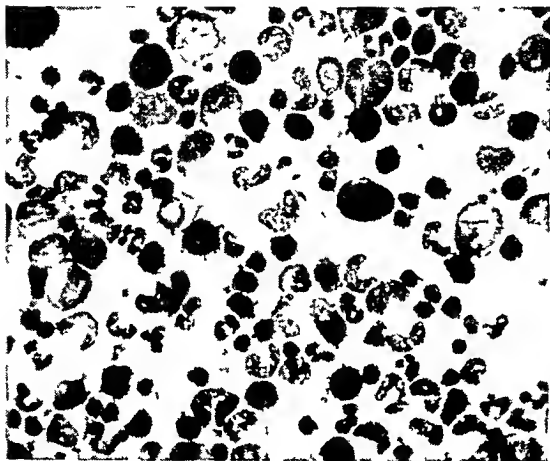
* (a) = Smears from trephine curettings

† (b) = Smears from puncture material

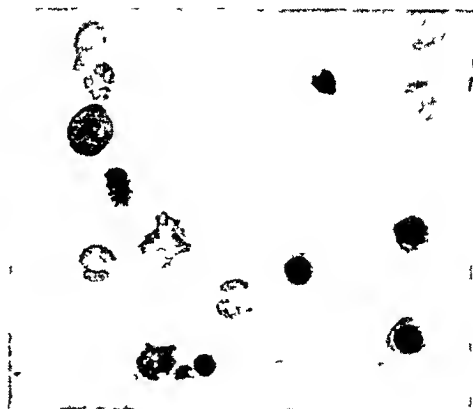
TABLE I—Continued

				Normoblasts			W B C							Retes	RBC WBC	
				"A"	"B"	"C"	P	P 2 and 3	My- elo- cytes	Blasts	His- tio- cytes	L	E			
11	Hugh McG	(a) (b)	Eg 97 78	Meg 233 100	21	45	55	88	160	102	17	18	20	39	1 122	
					80	106	94	124	248	114	10	12	28	51	1 13	
12	James L (Poor in cells)	(a) (b)	08 08	— —	104	336	48	34	190	124	10	04	32	78	1 1	
					36	172	72	74	350	146	06	—	24	46	1 25	
13	Armun L	(a) (b)				14	78	08	20	02	838	10			1 9	
						46	78	24	14	02	798	08	28		1 8	
14	Fred T	(a) (b)	08 06		89	219	73	74	197	169	14	27	25		1 16	
					48	128	46	138	306	118	14	04	32		1 34	
15	Nathan W	(a) (b)	02 04		26	172	106	110	322	138	10	04	40	65	1 23	
					40	114	36	124	360	174	12	24	32	30	1 30	
16	Barbara W	(a) (b)	92 20		126	114	80	56	152	190	20	08	16		1 14	
					172	70	12	246	234	78		04	28		1 14	
17	Abraham L	(a) (b)	08 12		34	96	450	44	226	124	10		06		1 67	
					50	172	130	120	366	74	10	02	06		1 150	
18	Zalman K	(a) (b)	23 04		43	243	237	13	220	167	40	Many Gaucher cells			1 08	
					40	154	90	68	230	182	88	64	80		1 34	
19	Arthur MacA	(a) (b)	140 28	496 330				57	186	93	08				1 06	
								150	242	242	08				1 18	
20	Harrison L	(a) (b)	20 10		82	268	386	34	90	4	3		14		1 33	
					42	136	206	166	188	34	46	74	6		1 15	

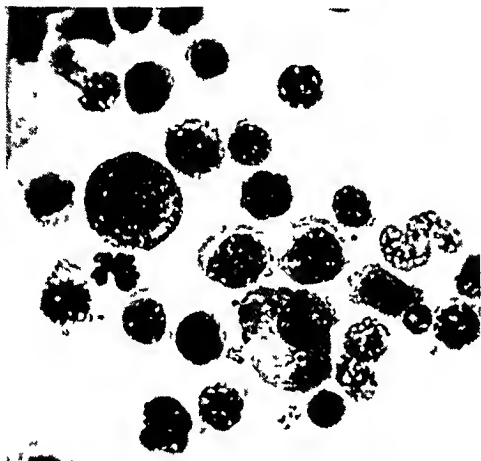
* (a) = Smears from trephine curettings
† (b) = Smears from puncture material



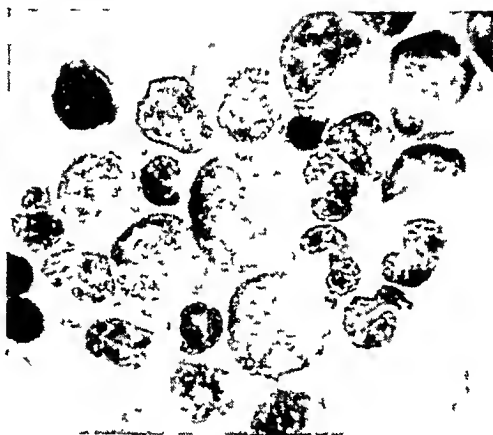
1a



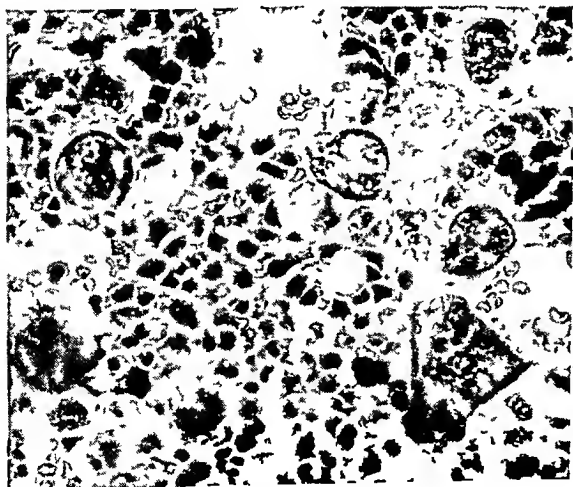
1b



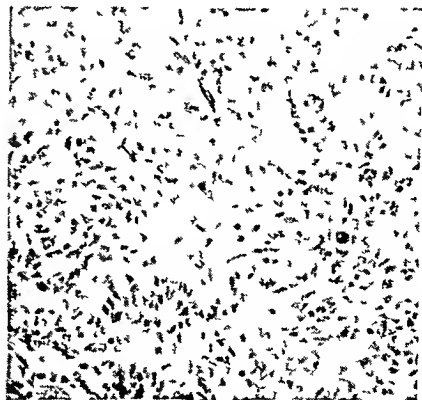
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3



4



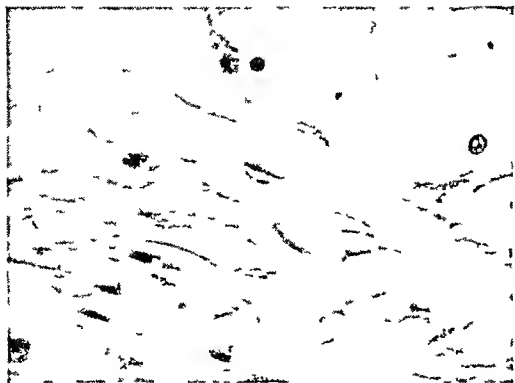
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cells, and the reticulocyte counts are presented in table 1. In three cases, the "puncture" smears were very poor in cells, making differential counting difficult if not impossible. This has frequently been our experience in other cases when only puncture was done and the same is noted in many of the protocols of both Nordenson⁸ and Segerdahl.⁷ In the "trephine" preparations, except in those cases with an acellular marrow, highly cellular preparations were always obtained. In the "puncture" preparations, the cells obviously arising from the marrow were relatively scanty as compared with the numbers of mature erythrocytes in the preparations, so that the picture usually resembled closely a blood smear either from a case showing leukocytosis or leukemia. Differential counting in these preparations was at times somewhat easier than in the "trephine" preparations in which the cells might be closely packed together, but one obtained the definite impression that in the one case one was dealing with blood containing a few marrow cells whereas in the other one dealt with marrow interspersed with some blood cells.

Ratio of Nucleated Red Blood Cells to White Blood Cells This ratio, which from previous studies had generally been found to be about 1 to 1 (with variations from 0.6 to 1 to about 1.5 to 1) is useful in estimating whether the granulocytic or erythroblastic cells predominate in a given preparation. It may be seen from the table that, although the ratio of red cells to whites was frequently substantially the same in both types of preparation (Cases 4, 5, 6, 11, 13, 16), in 14 cases it was different. In each of these cases, the ratio of nucleated red cells to white cells was definitely less in the puncture preparations. In several cases, the preponderance of white cells to reds in the puncture preparations was quite striking (3, 7, 8, 10, 14, 15, 18). These findings may be interpreted as signifying the failure of the primitive red cells to appear in large number in the "puncture" smears as noted below.

From table 1, one sees that in seven of the 20 cases, the most immature nucleated red cells (erythrogones, megaloblasts, normoblasts "A," "B") in the "trephine" preparations far outnumbered the same types of cells in the puncture preparations. In several cases the results obtained in the "puncture" preparations might well have been misleading in this regard. In Case 3, for example (pernicious anemia), megaloblasts were present in

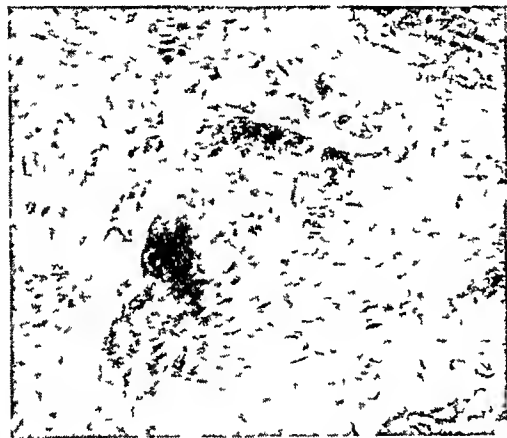
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- FIG 1a Sternal bone-marrow biopsy smear. Made directly from a bit of bone removed by trephine-curette method. Note large numbers of marrow cells present. $\times 500$
- 1b Smear. Made from puncture biopsy in same case. Note the scarcity of marrow cells and the large number of blood cells. $\times 500$
- 2 Trephine biopsy. Smear. Various types of nucleated red cells are seen. The smears are invaluable for study of individual cellular morphology. $\times 1000$
- 3 Trephine biopsy. Smear. Various types of granulocytes are seen. $\times 1000$
- 4 Trephine biopsy. Section. Polycythemia illustrating marked hyperplasia of megakaryocytes. Megakaryocytes are found only occasionally in puncture preparations. $\times 550$
- 5 Trephine biopsy. Section. Aleukemic reticulosis. The marrow is replaced by dense tissue. Smear preparations were worthless since they showed no cells. $\times 125$



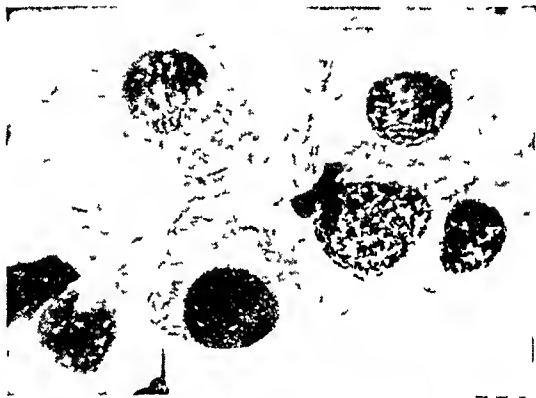
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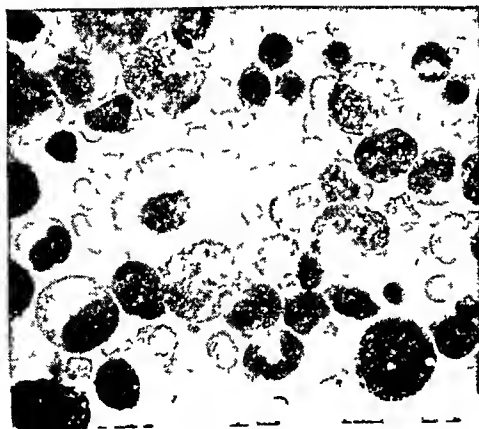
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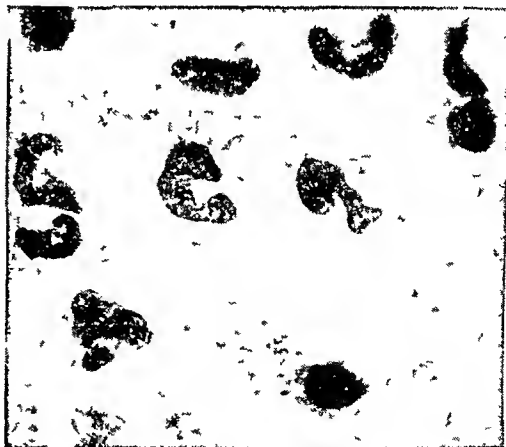
8a



8b



9a



9b

fair number in the trephine preparations and almost completely absent from the puncture preparations

Reticulocyte Percentage This was used as an index in demonstrating the relative maturity of the non-nucleated red cells in the trephine as compared with the puncture preparations and was determined in 11 cases. In nine of these the percentage of reticulocytes was greater in the trephine preparations, although in two cases (9 and 11), both of them examples of pernicious anemia under treatment, the reticulocyte per cent was greater in the puncture preparations

White Cells Although rather marked differences in the percentage composition of the white cells were present at times, no such striking disproportion between immature and mature leukocytes as existed with the erythroblastic cells could be seen, although in two cases (4 and 6) the percentage of myeloblasts in the trephine preparations was much higher than in the puncture preparations

Megakaryocytes These huge cells were commonly found in the trephine preparations, being seen only occasionally in the puncture preparations

B The Sections These were of course present only with biopsy preparations. Although artificial sections may be prepared from the puncture preparations by allowing the puncture material to clot and then sectioning it in the ordinary way, these were not made. As brought out in previous papers,^{4, 5} the sections are of value not so much for the examination and study of the individual cells as for the study of the topography of the marrow and its general functional state (hyperplasia, hypoplasia, etc.), the recognition of islands of proliferating leukemic or malignant cells, the relationship of islands of cells to each other and to adjoining reticulo-endothelial cells and for study of the megakaryocytes

Smear preparations, particularly those obtained by puncture, may show varying degrees of cellularity dependent wholly upon differences in technic. These differences may be so great that the distinction between hypoplasia and hyperplasia may be impossible. Thus, in Case 17 (benzol poisoning), the smears from both the biopsy and puncture preparations seemed to show an essentially normal number of cells, and yet the sections (figure 10) showed a striking degree of hypoplasia of most of the marrow with small islands of fairly normal cellularity. In Cases Mary C, Mitchell G, Edna S, Charles

FIG 2 6 Trephine biopsy Section Lymphosarcoma of spleen, metastasis to bone-marrow with fibrous tissue replacement. The smear preparations showed no cells. $\times 500$

7 Trephine biopsy Section Lymphosarcoma, metastasis to bone-marrow. Dense mass of tumor tissue present in one small area of section, not discovered in smear preparations. $\times 300$

8a Trephine biopsy Section Metastatic carcinoma of pancreas. Bone-marrow replaced by fibrous tissue. No malignant cells seen. $\times 300$

8b Trephine biopsy Smear The smears (same case as 8a) showed groups of primitive cells thought to be carcinoma. This was later confirmed by post-mortem examination. $\times 1000$

9a Puncture biopsy Smear Splenomegaly? cause Smears showed normal marrow cells with a rare large cell called a histiocyte. $\times 1000$

9b Trephine biopsy, same case Smear Large numbers of Gaucher cells present in the smears and sections making diagnosis readily possible. $\times 1000$

TABLE II
Smears and Sections

	Smear Preparations	Sections
Mary C	Diminished cellularity	Islands of leukemic cells
Mitchell G	No cells	Connective tissue replacement of marrow (lymphosarcomatosis)
Edna S	No cells	Aplasia of marrow
Charles M	Very few cells	Replacement of marrow by reticulum and connective and proliferating reticulum cells with giant cells (aleukemic reticulosis)
Eva S	Very few cells	Small localized area of lymphoblastic proliferation (lymphosarcoma)
Jacob H	Very few cells ? Islands of abnormal cells	Metastatic malignancy (carcinoma of pancreas) with connective tissue replacement of parts of marrow
Sylvia W	Hyperplasia of W B C <i>Diagnosis</i> Myeloid leukemia	Cellular bone-marrow ("Banti's disease")
Bessie D	<i>Diagnosis</i> Myeloid leukemia (Proliferation with primitive cells)	Hyperplastic bone-marrow, no unrestrained growth, islands of primitive cells surrounded by typical nucleated R B C <i>Diagnosis</i> Pernicious anemia
Maria B	Hyperplasia of myeloblasts <i>Tentative Diagnosis</i> Aleukemic myelogenous leukemia	<i>Diagnosis</i> confirmed by sections which showed islands of proliferating myeloblasts with invasion and destruction of R B C and megakaryocytes
Isadore L	Normal marrow	Hypoplastic marrow with small areas of normal cellularity No megakaryocytes <i>Diagnosis</i> Hypoplastic anemia (benzol poisoning)

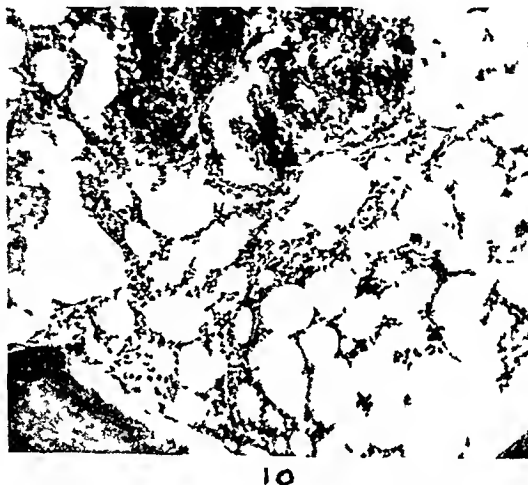
M, Eva S, Jacob H (table 2), very few marrow cells were found in the smear preparations. All of these cases presented anemia, leukopenia, and thrombocytopenia, and it was impossible to state at the time whether the absence of cells was due to faulty technic or to actual aplasia of the marrow. It was only when the sections were studied in these cases that the true pictures became evident: myeloid leukemia, fibrosis of the marrow following lymphosarcomatous invasion, aplasia, aleukemia reticulosis, lymphosarcoma invading the marrow, carcinomatous invasion, and fibrosis of the marrow.

When dealing on the other hand with an obviously hyperplastic marrow in the smear preparations, it is at times difficult to state definitely whether or not leukemia is present. Occasionally (Cases Sylvia W and Bessie D are illustrative) the diagnosis of myeloid leukemia had been made on the basis of apparently extreme myeloid hyperplasia. The sections, however, in the first case showed normal, although hyperplastic, islands of both red and white cells without destruction or replacement of erythroblastic or mega-

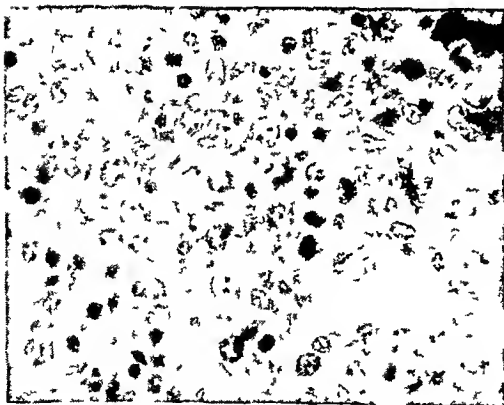
karyocytic elements ("Banti's disease") In Case Bessie D, the very primitive erythroblastic cells present (erythrogones) were mistakenly called myeloblasts, the sections showed islands of primitive cells, at the edges of which were easily recognizable erythroblastic cells i.e. pernicious anemia However, from sections alone, it is usually difficult if not impossible to distinguish between leukemia and pernicious anemia since both show large islands of primitive cells

COMMENT

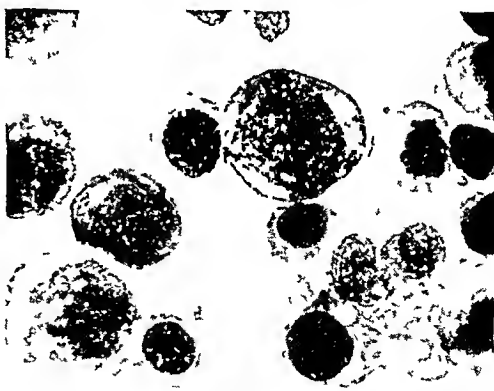
1 *Diagnostic Value of the Sternal Bone-Marrow Biopsy* During the past ten years, ample proof has accumulated of the diagnostic value of the



10



11a



11b

FIG 3 10 Trephine biopsy Section Hypoplastic marrow from chronic benzol poisoning Diagnosis made when bone-marrow findings were discovered Smears from both the puncture and trephine biopsies showed essentially normal findings Sections invaluable for topography and general idea of cellularity $\times 100$

11a Trephine biopsy Section Extremely hyperplastic marrow with many primitive cells erroneously diagnosed as myeloid leukemia $\times 500$

11b Trephine biopsy, same case Smear The smears showed many megaloblastic cells and deformed metamyelocytes typical of pernicious anemia The smears are essential for study of individual cellular morphology $\times 1000$

sternal bone-marrow biopsy Its chief use has been in the differential diagnosis of those cases presenting obscure and chronic anemia refractory to liver and iron Usually these cases are associated with leukopenia and thrombocytopenia This triad of hematological findings—*anemia, leukopenia, and thrombocytopenia*—may be due to many different conditions of the marrow Thus, the marrow may be almost completely destroyed by chemicals (benzol, gold, etc.), i.e. aplastic anemia, or by proliferating malignant or leukemic cells, or may be extremely hyperplastic as in pernicious anemia, aleukemic myelogenous leukemia, spleen-liver (Banti's) disease, and yet the blood picture may be substantially the same The frequent cases of leukemia with a low leukocyte count ("aleukemic" leukemia) have been a source of continued interest Although many of these cases show very abnormal differential leukocyte pictures with the presence of primitive cells (lymphoblasts, myeloblasts or histiocytes), not infrequently proved cases of leukemia show no changes whatever in the differential picture and are usually accompanied with an erythrocyte picture resembling pernicious anemia Macrocytic anemia may be present not only in the "liver deficient" states (pernicious anemia) but in many other totally unrelated conditions certain cases of hepatic disease, myxedema, chronic nephritis, leukemia, lymphosarcoma invading the bone-marrow, and in chemical destruction of the marrow Usually leukopenia and thrombocytopenia are also present The bone-marrow biopsy is especially helpful in unravelling the diagnosis in these cases and may show either a "full" marrow or a relatively "empty" one In many cases it has been impossible to predict from the blood picture and the clinical findings whether the marrow will be hyperplastic or aplastic, so that in certain cases considered to be aplastic anemia, leukemia or lymphosarcoma will be found, and when pernicious anemia is suspected a hypoplastic marrow may be discovered In six cases the anemia, leukopenia, and thrombocytopenia were due to widespread involvement of the marrow by lymphosarcoma It is felt, therefore, that when a patient presents chronic anemia accompanied usually with a lowering of the leukocyte and platelet counts, and is refractory to liver and iron therapy, a bone-marrow biopsy may help to clear up the diagnosis

2 *Critique of the Puncture Method, Limitations of Both Methods* The phenomenal increase of interest in the study of the bone-marrow may be attributed to the rapidly growing interest in the so-called blood diseases and in the knowledge that fundamentally these represent disorders of the blood-forming apparatus, chiefly the marrow So intense has this interest become in the last few years that various short-cuts have been utilized in the attempt to obtain information as expeditiously as possible One of these short-cuts has been puncture of the sternal bone for the removal of material which has been called marrow

The bone-marrow biopsy was first performed by Ghedini¹⁰ in 1908, trephining of the tibia being done This method languished for many years only a few investigators, chiefly Zadek² and Peabody,³ being bold enough

to continue drilling into such a heavily protected marrow. Furthermore, the tibial marrow was normally acellular and gave information only in such hyperplastic conditions as pernicious anemia. Trephining of the sternal bone as a much simpler maneuver was introduced by Seyfarth¹ in 1923 and was then slowly taken up. Custer and his co-workers¹¹ set up certain standards in biopsy of the sternal marrow such as those relating to comparison of its cellularity with that found in other bones. Puncture of the marrow with a hollow needle as introduced by Arinkin⁶ and as modified by many workers has aroused great enthusiasm. This is indeed laudable since it indicates a greater interest in the marrow than was previously present but it also calls for some warning as regards interpretation.

As Custer¹¹ has pointed out, it is often dangerous to conclude from examination of a small piece of bone and marrow removed from the sternum the condition of the entire marrow which in size probably compares with that of the liver. In a scattered organ like the marrow, local conditions vary tremendously. This criticism must hold even greater weight for the material removed by puncture of the sternum with a hollow needle. This material looks very much like blood when aspirated, when smeared, it is found to consist mainly of mature red cells with a variable number of marrow cells, dependent both upon local conditions in the bone and marrow examined and on the technic. The first 0.5 to 1 c.c. contains many more marrow cells than the remainder of the aspirated material, so that several authors warn against removal of more than 1 c.c. Some investigators prefer to remove only sufficient material with which to make a few smears.

That the material removed by aspiration is mostly blood is confirmed by comparison of the "puncture" smears with the "trephine" smears made directly from bits of bone removed by curette from the trephine cavity. These show, as brought out above, that the ratio of nucleated red cells to whites is usually far greater in the trephine preparations, that the reticulocyte percentage is almost always much greater, and that the relative proportion of immature nucleated red cells is usually much greater in the trephine preparations. These observations suggest a number of interesting points some of which have already been emphasized, namely, that the nucleated red cells are intravascularly situated, the white cells growing extravascularly, that the more primitive nucleated red cells tend to remain adherent to the underlying endothelial surfaces, making them difficult to remove by simple aspiration. This is confirmed by the experiments of Maximow¹² who was unable to remove the most primitive erythroblasts from the marrow even by repeated perfusion. The same explanation probably accounts for the fact that the white cells greatly outnumbered the nucleated reds in the great majority of the puncture preparations. The comparative reticulocyte count may be used as an index of the degree of dilution of the immature cells with blood cells. The fact that the reticulocyte count (except in two instances of pernicious anemia under treatment) was always higher in the "trephine" than in the "puncture" preparations suggests that the puncture material is

obtained from a "part-way station" located between the bone-marrow on the one hand and the blood on the other. It would therefore seem improper to label the material removed by sternal puncture as bone-marrow since it appears to be chiefly blood in which are present a variable number of marrow cells. "Marrow juice" might be a better term.

Other criticisms of the technic of puncture have already been mentioned above. These are perhaps more important from a practical standpoint than those just discussed, namely, that the puncture material gives no idea of the topography of the marrow, that it is frequently deficient in cells when the marrow is cellular, that the deficiency in cells may be incorrectly interpreted when the marrow has become fibrotic as the result of previous invasion by tumor or leukemia, that it may fail to show Gaucher cells, leukemic islands, or small masses of proliferating metastatic cells, and that the interpretation of a hypoplastic or hyperplastic marrow is frequently impossible.

The criticisms of the puncture technic should not prevent us from conceding to it its relative simplicity and ease of technic as compared with the relatively formidable technic of trephination. Aside from ease of technic, it has certain obvious advantages: its applicability to infants and small children and its use for several examinations of the marrow in a case under continued treatment or observation. We feel, however, that once the idea of biopsy of the marrow has been entertained, it should be accomplished by as good a method as we have at our disposal rather than to rely upon the more or less haphazard results obtained from puncture despite its simplicity.

From the foregoing, the impression should not be obtained that the bone-marrow biopsy when performed by the trephine method which we have utilized must always give perfect results. As with all diagnostic methods, errors may be made. These are ordinarily due to poor preparations which are occasionally obtained, or to incorrect interpretations. The findings in the marrow may be stretched to make a preconceived diagnosis. Experience, and particularly the bitter ones of demonstrated error, have led us to postpone a definite diagnosis unless both the sections and smears have been examined and correlated, this inevitably means a delay of several days for the sections, but this amount of patience has been found valuable. In the absence of either the smears or the sections or of good preparations, it is advisable to hedge on the diagnosis, unless the condition is clear-cut. The smears are of no value when the marrow is extremely hypoplastic or fibrotic. The sections, however, may mislead us into making a diagnosis of leukemia as, for example, in the extreme hyperplasia of pernicious anemia with the presence of large numbers of primitive cells and many mitotic figures. Study of the bone-marrow when dealing with large sections from autopsies is difficult enough, with the small bits of marrow removed from the sternum at biopsy, it is advisable to keep one's diagnostic enthusiasm in close check. It is gratifying to note that with continued attention to these points our percentage of errors has been diminishing materially from year to year. With due attention to details, with proper preparation of both the smears and

sections, and above all with proper interpretation of what is seen, the biopsy should well repay the effort entailed in its execution. The data obtained from puncture material must always be surrounded with reservations since they are based on the findings in a fluid of uncertain origin and of mixed content. For research study, as Jaffe has pointed out,¹³ the puncture biopsy is certainly not to be relied upon.

3 Indications for Sternal Bone Marrow Biopsy The most obvious and important indication for sternal biopsy is in the diagnosis of obscure hematological problems, particularly in cases presenting persistent anemia, leukopenia, or thrombocytopenia, either singly or in combination. Because the biopsy is a surgical procedure, although a simple one, it stands to reason that all the various other diagnostic methods of probable value should first be carried out. The diagnosis of a case presenting obscure long-standing anemia may lead one into all sorts of by-ways far afield from what is technically hematology, but this simply illustrates that this field cannot be divorced from clinical medicine, of which it is an integral part. When complete physical examination, studies of the blood, roentgen-rays of the chest, the gastrointestinal tract, and the bones have not been productive of a diagnosis, the sternal biopsy may solve the problem. One should, however, be prepared for disappointment, for occasionally even this procedure fails to clear up an obscure case.

Knowledge of the condition of the marrow may at times be essential preliminary to the serious operation of splenectomy. Is a given case "Banti's disease," warranting splenectomy, or is it aleukemic myelogenous leukemia which is best left alone? In a recent case presenting severe rapidly progressive macrocytic anemia, splenomegaly, icterus, a normal fragility test, and lack of response to liver extract, it was important to know whether the marrow was merely hyperplastic or showed invasion by leukemic or malignant cells. When only extreme normoblastic hyperplasia was found, the operation of splenectomy was done and was followed by a spectacular recovery. Lawrence and Knutti¹⁴ have pointed out that it might be worth while to note the condition of the megakaryocytes in a case of thrombocytopenic purpura prior to splenectomy since if the marrow were found to contain large numbers of these cells, the operation would probably prove successful, if megakaryocytes were few, splenectomy might be of no value. Splenectomy is occasionally done for "aplastic" anemia, it seems wise to be sure of one's ground before this major operation is done. The caution should be made that in the presence of a very low platelet count the biopsy should be performed with unusual care and possibly postponed until after a transfusion of blood is given.

Another indication for sternal biopsy is in the differential diagnosis of splenomegaly. Seyfarth, who originated the method while stationed at an institute of tropical medicine, first used it in the diagnosis of chronic malaria and kala-azar. He felt that the procedure did not carry with it the dangers of splenic puncture, with possible rupture of the capsule and resultant hemor-

rhage This possibility has also deterred us from utilizing the latter diagnostic method, although such observers as Pittaluga¹⁵ have performed splenic puncture without accident in several hundred cases The diagnosis of Gaucher's disease which may present splenomegaly as the only abnormality has been alluded to above The spleen and the bone-marrow are so closely interrelated that study of the marrow may thus yield valuable information regarding the more inaccessible organ

A final indication for the sternal bone-marrow biopsy is in the research study of various hematological problems, the ultimate rationale being the gradual development of knowledge regarding their physiological pathology Studies of this type have already added to our understanding of the effects of liver therapy in pernicious anemia, and of aminopyrine in producing maturation arrest in agranulocytosis¹⁶ Many other problems remain to be worked out Again, the hope is expressed that hit-or-miss methods should not be tolerated

SUMMARY AND CONCLUSIONS

The diagnostic value, indications, and limitations of the sternal bone-marrow biopsy were discussed In 20 consecutive cases, the trephine and the recently popularized puncture methods for biopsy of the sternal marrow were compared With use of the trephine, two types of preparations are obtained sections made from the removed plug of bone, and smears made from bits of bone removed from the edges of the trephine opening With the puncture, a sanguinous appearing material is aspirated, from which only smears can be made

A comparison of the smears made with the "trephine" and the "puncture" methods showed a far greater cellularity in the biopsy preparations, a greater reticulocyte percentage, a greater number of erythroblastic cells relative to granulocytes, and a greater number of early nucleated red cells The puncture preparations frequently consisted almost entirely of red blood cells interspersed among which were some marrow cells The sections obtained at biopsy not only gave one an idea of the general topography of the marrow, but of its general degree of cellularity, the presence or absence of islands of leukemic or neoplastic cells, and in certain cases of connective tissue replacement Combined study of the sections and of the smears has proved to be of much greater value than study of the one type of preparation alone

Puncture biopsy of the sternum is to be criticized because the material obtained is usually not marrow but a variable mixture of blood with marrow cells ("marrow juice"), because lack of cellularity in this aspirated material does not necessarily mean lack of cellularity in the marrow itself, because primitive erythroblastic cells, present in the marrow, are frequently not obtained, and because abnormal islands of neoplastic and leukemic cells are either not obtained or if seen may be misinterpreted because of the lack

of topographical relationship The chief advantage of puncture biopsy is its simplicity, but this is greatly outweighed by its inaccuracy When the procedure of bone-marrow biopsy is contemplated, we feel it should be done in as careful a manner as possible since, even with the best technic, interpretation may be difficult

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NEUROLOGIC MANIFESTATIONS IN "HYPOGLYCEMIC SHOCK" (SAKEL)

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PRESENT attempts to treat schizophrenia and other psychoses with hypoglycemia induced by large doses of insulin, afford the opportunity of observing at one's leisure, many interesting neurological manifestations seldom otherwise witnessed

Through the courtesy of Dr. John R. Ross, Superintendent of the Harlem Valley State Hospital, N. Y., and the kindness of Drs. I. Murray Rossman, William B. Cline, Jr. and O. Schwoerer of the male service and Dr. A. Goulacher and Dr. Pellens of the female service I was among those privileged to observe this phase of their work on the "Insulin Wards." The method used was that of Sakel who had personally trained the staff during his stay at the Harlem Valley State Hospital. Their scientific and conservative attitude left a lasting impression of the reliability of their evaluation of the treatment, which we hope will soon be published. We witnessed most encouraging results in a group of patients characterized by Dr. Sakel himself as "deadwood" and offering little expectation of improvement. I am sure that these interesting results will be reported in detail by those in charge of the work at a later date.

Many of the manifestations which accompanied the hypoglycemic state were of particular interest to the neurologist. These neurological pictures were so varied and striking in their combination and appearance that in all probability they are now being seen for the first time in this condition of severe hypoglycemia. In my experience, none of these have been described in accidental hypoglycemia arising as a complication of diabetic treatment or as a symptom of pancreatic adenoma.

I found it useful for my own comprehension of these complicated neurologic events to arbitrarily divide them into three categories, namely:

(1) "Prolonged" manifestations which were those occurring for a longer period during the four to five hours of treatment,

(2) "Sudden" manifestations which were those which occurred suddenly and usually toward the end of the treatment.

(1) The "prolonged" manifestations

Soon after the insulin had been given, the patient ordinarily remained quiet and resting. During the second hour, when diaphoresis usually was well established, there would ensue either somnolence, restlessness, mild

* Received for publication August 9, 1937

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excitement, or shouting. This usually passed off as the hypoglycemic state progressed into deeper coma. In this phase one could observe

(a) Quick, jerking movements of the arms, legs, body, and restless tossing of the head. A sudden flexion, but less frequently extension of both arms was extremely common. These movements often recurred for an hour or more during the treatment and as often as 15 to 20 times per minute, although the rate varied greatly. Touching or shaking the patient frequently initiated such "flexor arm jerks."

(b) Some patients exhibited prolonged sucking movements of the lips. No special emotion could be noted in the facial expression during these movements. At times, there was marked grimacing of the face accompanied by bilateral athetoid movements of the extremities.

(c) There were episodes initiated by flushing of the face, dilation of the pupils and labored breathing. These were associated with rigid extension of the lower extremities, bilateral adduction and extreme internal rotation of rigidly held arms. The wrists were rotated to hold the palms outward. The fingers were most often tightly clenched into the palm with the thumb projecting characteristically between the index and middle finger, or the ring and middle finger. The eyelids were often retracted widely, producing a picture of extreme fright. The whole movement was slow and rhythmic. After about thirty seconds to one minute the arms and legs would relax and resume a neutral position until the next movement began again. This picture at its climax, clinically suggested the attitude of decerebrate rigidity.

(d) There occurred at times only a partial manifestation of the above. The arms would rotate, the palms face outward, but the limbs would remain fairly well relaxed and this position would be maintained for long periods without any interruption.

(e) Irregular, thrashing, apparently purposeless movements of the arms and legs were frequently noted. At times there seemed to be definite attempts to brush away the physician's arm or the towel on the patient's forehead. These movements suggested true defense reflexes. The patient would often strike the bed, the wall, or his own face during this activity.

(f) The deep reflexes were difficult to evaluate because of the constant spasms in the extremities which interfered with their elicitation. However, following the somnolent stage, the Babinski reflex would appear and then become sluggish as the patient approached deeper coma. The corneal reflex also disappeared in the later stages of coma. More often the Babinski appeared as part of a general flexor withdrawal reflex but toward the deeper stages of coma it could be elicited alone before its final disappearance in deepest hypoglycemia. Its appearance or disappearance apparently mirrored the depth of the hypoglycemic shock.

(g) Slow "trombone like" movements and irregular jerks of the tongue often were seen. A spontaneous clonus of the lower jaw, and clonic movements of the upper eyelids sometimes appeared for a short while.

(h) The extremities sometimes assumed a posture resembling that seen during the movements of dystonia musculorum or athetosis, however, they remained fixed in these positions, suggesting the term "frozen athetoid movements" for their description. Dr Dussik told me of seeing true hemiballistic movements as well as athetoid position of the hands in his Vienna material.

(i) Transitory hemiplegias sometimes occurred. Drs Cline and Schwoerer told me of seeing a hemiplegia which lasted for nine hours. I observed several transitory hemiplegic states. In one instance, a case on Dr Goulacher and Dr Pellens' service showed a transitory palsy of the left side of the face which preceded an epileptic convulsion.

All the movements and postures just described were most often bilateral but at times unilateral.

(2) "Sudden" neurologic manifestations

(a) Convulsive seizures frequently occurred and could be clearly recognized from the other convulsive movements of a more prolonged character in most instances. It was often difficult for me to decide exactly when a series of convulsive movements could be grouped as a seizure. The definition of what constitutes a true epileptic seizure is still highly unsatisfactory. Certainly if we call mild disturbances of consciousness with slight twitching a petit mal attack in everyday medicine, it then becomes quite difficult to state that a series of severe convulsive movements in an unconscious patient is not a true epileptic seizure. Sakel himself uses the term in a rather indefinite way, and so do many others.

(b) There occurred in about a dozen instances according to the doctors a sudden dramatic complication usually toward the end of the treatment, one of which I witnessed. Three cases were of great severity while the others were said to have been milder. These alarming manifestations of such a severe complication were particularly frightening to the onlooker when seen for the first time. Drs Rossman, Cline and Schwoerer felt that their observation may represent a specific type of complication with special prognostic features. Dr Dussik stated that in his experience it had occurred only five times in about 5000 treatments. It usually appeared as follows. When the regular proceedings for the termination of the hypoglycemic state had been instituted, the patient would fail to react. By previous experience the doctors had found that if such a patient did not react in 45 minutes even when intravenous glucose had been given, trouble was in all probability to be expected. The patient at the time was often noted to have very small pupils, which then slowly dilated and were associated with marked flushing of the face. There then ensued an excited phase with convulsive movements, contortions, rigid attitudes and extremely labored breathing lasting for 15 to 20 minutes. This phase was so severe that the patient appeared to be in extremis and completely exhausted. The movements would then slowly subside in severity and duration, the pupils return to more normal size, and the patient relax in apparent exhaustion.

with shallow slow respiration. After a lapse of 10 to 20 minutes another active phase would begin, augment to a frenzy of labored irregular movements and again subside. These alternating periods of activity and relaxation at times continued for one to two hours, diminishing in duration and severity with each attack.

It seemed as if the whole central nervous system was thrown into a frenzy of disorganized activity. There were recognizable hemiplegic attitudes, extrapyramidal manifestations of transitory cog-wheel rigidity, and signs of midbrain involvement in disturbed extraocular movements—the eyeballs moving asynchronously. There were also signs suggestive of disordered thalamic and medullary control of temperature, pulse and respiration, which appeared entirely disassociated from their usual relationship. For example, the temperature being 104.2° F, the pulse would be 160 and the respirations as high as 80 per minute. There were in addition manifestations of overactivity at the lowest levels of the brain stem as judged by the occurrence of opisthotonus and the attitudes of decerebrate rigidity. There was also evidence of overactivity in the autonomic nervous system, the dilation of the pupils, flushing of the face and rapid pulse as sympathetic overactivity, the contraction of the pupils and pallor as parasympathetic overactivity. It was extremely difficult to separate these rapidly changing pictures and fit them into neurological schemes. The general impression was that of an overactive, totally disorganized central nervous system being thrown into activity in a rhythmical manner. It suggested to me the term “neuro-physiologic crisis.” All of the neurologic manifestations, in spite of their severity, were reversible in character and the patient awoke from his hypoglycemic coma with no trace of the “neurologic storm” through which he had passed. He then would ultimately quiet down and remain stuporous. After full awakening he would still show some evidence of mental confusion for many days and at times as long as two or three weeks. The doctors had made the interesting observation that patients who experienced this severe complication usually emerged from this confused afterstate with definite signs of progressive improvement.

It is at present difficult to understand what occurs during this hypoglycemic treatment and what sort of nervous involvement produces these neurological pictures. Speculation, in the present state of our knowledge, may be interesting but is quite valueless. A great deal of work must be done. We hope that future study and evaluation of the hypoglycemic therapy may disclose some information which might help us to explain these unusual neurologic states. Until then, we must be content with close observation and careful recording of data.

MOTOR INVOLVEMENT OF THE CENTRAL NERVOUS SYSTEM IN PELLAGRA, A REPORT OF 2 CASES¹

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NERVOUS and mental symptoms are conspicuous in textbook descriptions of pellagra, but only the more extensive studies describe motor disturbances other than peripheral neuritis. Hemiplegias and paraplegias are described as being rare and generally occurring in the severe and terminal stages. Grinker¹ in a recent textbook states briefly that a picture similar to the neurological complications of pernicious anemia may appear but are never as severe or progressive. He states further that the lesions of the nervous system in pellagra are "not irreversible."

With newer methods of treatment, especially with new forms of diet and vitamin concentrates, the severe and so-called incurable phases of pellagra can be cured² and profound disturbances of the central nervous system reversed. The cases here presented, one resembling hemiplegia and the other diplegia, were totally disabled and even "helpless," one for three weeks and the other for six weeks. With intensive dietary treatment both became well. In each case chronic alcoholism was the obvious predisposing cause of pellagra, but it is now generally believed that "alcoholic pellagra" and endemic pellagra are the same disease. In 1928 Klauder and Winkelman³ reported finding "central neuritis" in every case of pellagra which they examined histologically, a total of 11 cases, and in many cases of alcoholism in which a diagnosis of pellagra had not been made.

The remarkable recovery of the patients here described, when treated as pellagrins, suggests that the motor involvement was really part of the pellagra syndrome.

CASE REPORTS

Case 1 L C, a 48 year old Negro laborer, was admitted to the Medical Service of the Cincinnati General Hospital April 18, 1936, complaining of "fits" of two days' duration. He gave a history of two similar attacks 10 years previously, and of alcoholism, up to one pint daily, for years. During the three months prior to admission he noticed loss of appetite, soreness in the chest and abdomen, slight loss of weight and aching and weakness in the lower extremities. The day before admission he had two generalized convulsions which he could not adequately describe, even though he claimed he was conscious throughout the "fit."

Physical examination revealed a fairly well developed, fairly well nourished Negro

¹ Read in part at the Ninth Annual Meeting of the Central Society for Clinical Research, Chicago, Illinois, November 6, 1936

who was restless, disoriented, confused, at times delirious, and who made purposeless choreiform movements of his arms and legs. His lower extremities were weak and he was unable to walk. The right pupil was irregular and larger than the left, both reacted only slightly to light. The skin and mucous membranes showed the diagnostic signs of pellagra. The margins of the tongue were smooth and red, and areas of leukoplakia were present beneath the lateral margins. The gums and oral mucous membranes were also red and beefy. The skin showed increased pigmentation, roughening and desquamation of the dorsum of the hands, and of the feet, elbows, and knees. The lesions of the hands were sharply demarcated from the healthy skin of the forearm. Examination of the central nervous system showed knee jerks which were thought to be normal. Ankle, abdominal, and cremasteric reflexes were absent. There was no ankle clonus or Babinski reflex. Sensory examination was impossible. Blood pressure 130 mm of Hg systolic and 80 diastolic.

Laboratory Findings Hemoglobin 80 per cent (Sahli), red blood cells 3.9 millions, white blood cells 14,000 with 82 per cent neutrophils. Urine Specific gravity 1.032 (later becoming normal), sugar and albumin 1 plus, many granular casts. Later examinations were negative. Blood Kahn test negative. Spinal fluid examination negative, except for positive protein on admission, later examinations were normal. Gastric analysis following Ewald meal 24 per cent free HCl, 54 per cent total HCl. Blood sugar, blood urea-nitrogen, and carbon dioxide combining power were normal.

Progress During the first two days of hospitalization the patient had 18 or 20 "convulsions," each consisting of clonic twitching of the extremities, usually of the lower extremities only, accompanied by opisthotonos, incontinence, and striking mental excitement. He was not unconscious during these attacks. For several days after admission he was delirious and uncooperative. Incontinence of urine and feces persisted for six weeks after admission. He did not have diarrhea at any time during the course of his disease. Treatment with a high caloric, high vitamin diet, intramuscular liver extract and brewers' yeast induced definite and rapid improvement in the dermal lesions, tongue, and mental state of the patient. He continued, however, to show marked motor incoordination with a rigidity so great that he was unable to leave his bed or to feed himself. At times his picture suggested a left spastic hemiplegia. On May 11 (twenty-fourth hospital day), he was examined by Dr. H. D. Fabing of the Division of Neurology who found spasticity of the left arm with hyperactive reflexes, absent reflexes in both legs, fascicular twitching in all muscles, Oppenheim on right and Gordon on left. He made a diagnosis of "toxic encephalopathy with left sided focal signs." Dr. Fabing again saw the patient on June 3 (forty-fifth hospital day) and described slight left facial weakness, increased deep reflexes on the left, bilaterally absent ankle jerks, bilateral Gordon, Oppenheim on the right, groping movements of the hands, and speech containing jargon. His interpretation was "Diffuse encephalopathy (demyelinating) with 'pellagra,' with a suggestion that there might be accompanying peripheral neuritis."

Rapid improvement continued and 11 weeks after admission, the patient was discharged. At that time he was mentally clear, and was able to walk about the ward rapidly and without help. However, he still complained of inability to use his legs as well as formerly and there was slight residual rigidity of the left arm. Eight months after discharge an investigator learned that he had gone South to his old home to look for work, supposedly well.

Case 2 T. C., a 28 year old negress, was admitted to the Psychiatric Service of the Cincinnati General Hospital May 12, 1936 in a state of mild delirium.

Present Illness During the four years preceding admission, this patient had been consuming large amounts of strong alcoholic beverages. Her sister described two previous spells of extreme nervousness accompanied by visual hallucinations.

During the three months prior to admission, she had become progressively weaker and, because she was "unable to prepare her meals," had been eating a diet which her sister felt was deficient. Two days before admission she suddenly screamed and began to make purposeless movements and meaningless sounds. Soon afterwards she had visual hallucinations. This condition persisted until admission.

Physical examination showed a well developed but poorly nourished black female who was oriented only intermittently as to time and place. She refused to answer questions and made slow purposeless movements of her entire body, head and extremities, and picked at her clothing, breasts, vulva, and anus. At times she sat up in a bizarre manner. The skin showed diagnostic signs of pellagra,—namely, rough, desquamating dermal lesions were present over the hands, wrists, feet and ankles. The tongue and mucous membranes were normal. Reflexes were equal and active, no plantar reversal. Temperature 99.2° F, pulse 96, respirations 20. Blood pressure 135 mm of Hg systolic and 90 diastolic.

Laboratory Findings Red blood cells 4.63 millions, hemoglobin 80 per cent, white blood cells 12,000. The urine was normal, the blood Kahn test strongly positive, and the spinal fluid negative. Gastric analysis showed no free hydrochloric acid before or after histamine.

Progress For several days after admission the patient continued to be mentally disorganized, restless, and to have hallucinations and periods of intense fear and severe insomnia. These symptoms fluctuated considerably from day to day. She became unable to walk and was incontinent of urine and feces. Neurological examination revealed peripheral tenderness, great incoordination, and striking bilaterally symmetrical rigidity, especially of the legs. Through the courtesy of Dr. E. A. North of the Division of Psychiatry she was seen on her seventh day of hospitalization by the author who concurred in the diagnosis of pellagra. Treatment, which had been started on admission, consisted of a high caloric, high vitamin diet, dry powdered brewers' yeast, parenteral liver extract and moderate sedation. She improved rapidly and within three weeks she was able to feed herself and could walk moderately well, although spasticity of her legs persisted and she was still mentally confused. Despite the fact that she was known to be chronically addicted to alcohol, she was not classed by the psychiatrists as definitely of Korsakoff's syndrome and no opinion other than the diagnosis of pellagra and chronic alcoholism was offered as to the cause of the striking motor disturbances. On her twenty-seventh day of hospitalization (6-8-36) she was transferred to Longview Hospital for the Insane. Upon discharge from that institution 10 weeks later, she had no abnormal motor behavior, could walk rapidly with perfect coordination and was mentally clear. When seen one year later, this patient stated she was no longer drinking, she appeared to be in excellent health, and had had no return of symptoms since leaving the hospital.

COMMENT

Two adults who had motor involvement of the central nervous system at a time when they had diagnostic pellagrous lesions are presented in the present report. Both patients were addicted to alcohol. They had severe motor disturbances characterized by rigidity, inability to walk, and slow choreiform movements. The paralysis in one case was hemiplegic in type, while in the other it was paraplegic. Following the administration of a high caloric, high protein diet and large amounts of powdered brewers' yeast, the pellagrous dermatitis disappeared and the motor function of the central

nervous system was restored in both cases. The observations in this report show that motor involvement of the central nervous system, like glossitis and dermatitis, is part of the syndrome of pellagra and responds as do these symptoms to antipellagric therapy.

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NUTRITIONAL DISTURBANCES OF THE EXTREME SOUTH *

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KNOWING the life long interest that Dr Pratt has had in dietetics, the keen enthusiasm he has shown on the subject of nutrition, and appreciating the magnificent dietetic facilities that he has organized in his clinic, it seems appropriate to present some observations on the nutritional disturbances that are observed in the far South

There is considerable variation in the type of patients seen in the wards of a large general hospital in the South as contrasted with the wards of a Northern metropolis In the North it is customary to see many cases of rheumatic heart disease, for example, but in the South these cases are relatively rare True lobar pneumonia is an exception in the South and never are cases observed in large numbers at one time as they are in the late winter in northern climates On the other hand, there are seen in the South patients who have sprue, who have pellagra, who have malaria, amebic dysentery, bacillary dysentery and other types of disease which are relatively infrequent in the North Many of these disorders are representative of the so-called tropical diseases but actually diseases observed in the tropics, or the sub-tropics as is New Orleans climatically, are pretty much the same diseases that are seen in temperate climates The difference is merely quantitative rather than qualitative More cases are seen probably of sprue or pellagra in the South and fewer cases of pneumonia than in the North, but as many cases of hypertensive heart disease or of syphilis are seen in the tropics as are seen in the North As brought out recently by Haines, sprue is very much more common in the North than it was thought to be at one time Alcoholic pellagra is observed repeatedly in the North At one time the population of Philadelphia was almost decimated by malaria Amebic dysentery is ubiquitous Leprosy is world wide in its spread Really it might be said that, with the exception of certain dermatologic conditions, diseases of exclusively tropical distribution are almost non-existent

Just as the so-called tropical diseases are more frequent in the South than in the North, likewise there is another group of cases which seem to be commoner in this southern section of the country than elsewhere Perhaps this impression is erroneous and the apparent greater frequency of these disorders depends upon our searching for them more carefully and being more on the watch for them than in the past These disorders are

* Received for publication August 3, 1932

dependent upon some nutritional inadequacy. They exist as clear-cut, definite entities which depend upon such extrinsic causes as faulty diet or they may, on the other hand, be dependent upon some inherent defect in the organism as in pernicious anemia. The clear-cut syndromes may develop as result of vitamin insufficiency, inadequate and improper mineral intake or a lack of protein. It is my purpose to illustrate succinctly the expressions of some of the clear-cut definite entities and how they can be handled and then to discuss rather briefly the indefinite ill health which may be associated with nutritional faults which do not produce actual nosologic entities.

PELLAGRA

In Louisiana the incidence of pellagra waxes and wanes but on the whole it seems to be less common than it was a few years ago. It is surprising how severely ill some of the patients are who come into the Charity Hospital suffering from pellagra. It is also astonishing how these people sometimes fail to respond to what is now considered to be more or less a standardized treatment. Illustrating this is the case of Mrs. A. who was brought into the hospital June 1937 with a severe diarrhea. She had been confined to bed for some weeks, she showed very little dermatologic reaction, her mentality was distinctly obtunded. This woman was markedly undernourished, dehydrated, with extremely sore mouth and with a proctitis and extremely severe vaginitis. She was given fluids by vein, a high caloric-protein diet largely liquid on account of the stomatitis, powdered brewers' yeast, vitamin concentrates and even liver extract hypodermatically. In a few days improvement of the mouth and of the mental state was quite decided. The proctitis and vaginitis showed no signs of improvement. The diarrhea was controlled. In spite of temporary improvement the patient relapsed and died a few days later. This patient had in her diet an over abundance of the important elements, the lack of which may play a part in the production of pellagra. In spite of this, death occurred rather promptly. It is most discouraging in patients of this type to carry out the indicated lines of therapy and to get no result, but these cases are quite common. Incidentally it might be noted that the so-called alcoholic pellagra is rather uncommon in our wards.

PERNICIOUS ANEMIA

The most remarkable feature of pernicious anemia that I have observed in a woman's ward is the extreme degree of anemia these people have when they come into the hospital. It is perfectly astounding. A large number of these patients are seen. Illustrating the statement as to the severity of the anemia, is the case of Mrs. B. who entered the hospital on account of weakness, loss of weight and loss of appetite. This woman had been sick about six months. On admission to the ward she had a red cell count of about 1,000,000, hemoglobin 3.67 grams, mean corpuscular volume of 134

cu mm but no absence of free HCl Parenteral administration of liver extract brought about a sharp reticulocyte response and improvement took place very rapidly When discharged from the hospital in about a month the blood count had reached practically normal figures, mean corpuscular volume approached normal and in every way the patient was to all intents and purposes entirely well

Unfortunately on account of lack of financial resources and because many of these patients live in country districts where the free clinic is not available, they leave the hospital in excellent shape and return again in a period of about six months to a year or two almost as anemic as they were when they first entered We can build them up again, out they go and then sooner or later they return I had one patient who has been in the hospital seven different times, admitted each time with a high degree of anemia and each time she goes out in excellent condition

Unlike pellagra, pernicious anemia is a most satisfactory disease to treat Since the introduction of liver extract I have not observed a single death of a patient from this disease

SPRUE

In a hospital ward of 21 beds which are always filled, probably four or five cases of sprue can be expected during the year One of the cases that I have observed was that of Mrs S who went into the hospital with severe diarrhea, stomatitis and an extreme degree of emaciation, weighing 59 pounds I am recounting this case because I have kept in constant touch with her for nearly eight years and she is apparently well Mrs S was placed upon a diet consisting largely of bananas and raw pancreas After many days of encouragement to get her to follow this regime she was finally able to eat about two or three dozen bananas a day, her improvement began at this time After a period of six months she had more than doubled her weight The diarrhea disappeared and the anemia had gone She now retains a weight of 130 to 135 pounds and has continued to eat bananas to the extent of three or four a day From time to time she has slight diarrhea and as soon as this develops she takes a dozen or two dozen bananas and restricts her diet almost entirely to this article of food In a day or two the diarrhea will have gone and she is back again to normal health This patient never had liver extract Nowadays we are including with the banana diet injections of liver

Sprue was at one time thought to be solely a tropical disease but Haines calls attention to the relative frequency of sprue in North Carolina, and Snell records nine cases appearing at the Mayo Clinic in one year Undoubtedly sprue has been often misdiagnosed as pernicious anemia It is important to make the correct diagnosis because, as Haines writes, these patients with sprue can be cured if the proper diagnosis is made and if proper treatment is instituted they will not have to go through life living on liver

SCURVY

Once in a while I see obvious cases of scurvy but they are relatively rare. On the other hand, subclinical scurvy is by no means uncommon. A young pregnant woman was admitted to my ward with petechiae and a story of having had hemorrhages, small in amount, from the mouth and from the rectum. The blood studies were entirely negative. Although she had been taking vitamin C to a limited extent she, as every pregnant woman, required a superabundance of vitamin C which she had not been getting. The purpura cleared up and there was no further hemorrhage after giving her large quantities of orange and tomato juice.

BERIBERI

In a group of Louisianans who are poverty stricken the diet consists largely of red beans and rice. These people often develop beriberi. Such patients are seen from time to time so that we are always on the watch for it and are not surprised when these cases appear. A young person came into the hospital with an atrocious mouth, Vincent's angina. Several weeks prior to the development of the mouth condition there was marked weakness of the legs and some anemia. The condition became very much exaggerated when the patient was unable to eat on account of his sore mouth. Upon historical and physical examination the typical symptoms and signs of mixed beriberi were found to be present. After curing the mouth condition, the institution of a diet which contained vitamin B to excess promptly relieved the symptoms. From time to time I have seen patients who have recurrent attacks of beriberi. It may be noted that improvement is prompt and satisfactory after the first or second attack. The subsequent attacks fail to respond to treatment and the patient may be left permanently crippled.

PROTEIN DEFICIENCY

Quite commonly there is observed among our clientele patients who have voluntarily, or through poverty, restricted their protein intake to a point where anemia develops and even edema ensues. These people do not have edema as a result of depletion of plasma proteins through a nephritis or a nephrosis, but merely as a result of insufficient intake. Probably the most outstanding case was that of a young woman who had been advised by her physician, on account of a gall-bladder disorder, to withhold proteins. Conscientious and faithful in observance of the doctor's orders, this woman for a period of six months stopped eating every type of protein. When she was first seen she had marked edema of the legs, so marked as a matter of fact that she had some difficulty in getting about. There was complete reversal of the serum albumin-globulin ratio and serum albumin was well below edema levels. She was given a dozen eggs in the course of the next 12 hours and the diuretic effect was astounding. Edema quickly disap-

peared and since then she has had no further trouble. As in every general hospital a certain proportion of the people are admitted on account of extreme inanition. It is not uncommon to find these people with varying degrees of edema which disappears when they are given a well rounded diet.

CHRONIC DIETARY DEFICIENCY

Excluded from this group are those patients whose diet contains ample energy requirements, likewise those people who have some distinct and definite disease which may account for an excessive expenditure of energy, such as exophthalmic goiter, or who lose ingested food through the alimentary tract as the result of diarrhea. The patients of the group, to which I am referring, are not, strictly speaking, undernourished, but their body weight is subnormal and they have a variety of symptoms which may be attributed to an illy balanced diet. To those symptoms Sodeman and I have applied the term chronic dietary deficiency. These patients do not present clinical entities which have a nosologic significance. Possibly many of the cases might be called subclinical forms of diseases such as beriberi or scurvy or what not. Rather than mentioning specific instances which are extremely common in our section of the country, it may be more appropriate to run over briefly some of the expressions of this type of disorder. These people are usually thin, and anemia is a constant concomitant. We have seen patients who have macrocytic anemias yet do not have pernicious anemia, but more common is microcytic anemia. Some of the signs and symptoms that they present may be due to vitamin A deficiency, such as photophobia and dry skin. Gastrointestinal symptoms are common with dyspepsia, anorexia, constipation. There may be nervousness, headache and irritability. In younger individuals growth is impaired, dental caries may be observed and gingivitis with bleeding is common. They often have susceptibility to infection and vague aches and pains. They have ease of fatigue and weakness. Paresthesia and tingling of the extremities are by no means uncommon. These patients may have the features of the neurotic and the complaints of the neurotic. An analysis of the diet of these patients with chronic dietary deficiency, and a complete dietary history will show that they restrict the protein, fruits and fresh vegetables in their diet, through poverty or idiosyncrasy. Butter fat may disagree with them and they often eliminate that from the diet. Frequently their main article of food is carbohydrate. They live on what I have termed a "white diet." If these individuals, usually for economic reasons unable to pay for a well rounded diet, can be given a liberal supply of fish, meat, eggs and cheese, irradiated evaporated milk, fruits, tomato juice and cod liver oil, their improvement is sometimes astounding and the disappearance of the so-called neurotic symptoms is almost miraculous. Strange to say, chronic dietary deficiency is rarely observed in the negro, although they are the poorest section of our population. However, to the negro food is the first thought in his mind.

when it comes to spending his wages, whereas other considerations such as where and how he lives, how he clothes himself and so on are entirely secondary

CONCLUSIONS

No attempt has been made to detail systematically the nutritional disorders that are observed in the South. The more common ones have been discussed in a general and rather informal way. These disorders are extremely common and are most satisfactory to treat, with this proviso, and it is a big one, that funds be available to supply the patient with the proper foods

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COFFEE AS A CAUSE OF CARDIAC PAIN

By ROBERT L. LEVY, M.D., F.A.C.P., *New York, N. Y.*

THERE are many disturbances, both anatomical and physiological, which may cause pain in the region of the heart. To differentiate them and, in a given case, to determine the particular condition giving rise to discomfort, is the first requisite in diagnosis. The accurate definition of etiology often makes possible the distinction between a mild and a grave malady, it is essential for the institution of effective therapy.

As a cause of cardiac pain the drinking of coffee has received but scant attention, though briefly mentioned by some of the older clinicians. For example, Kiehl¹ states that "poisoning by coffee may cause more complete systole of the ventricles, palpitation, oppression and anginoid states." He ascribes these effects to two causes: first, to direct stimulation of the heart, and second, to more forceful contractions which represent a compensatory reaction to peripheral vasoconstriction. Allbutt² remarks that "coffee drinkers, and some nervous persons are liable, especially in later life, to attacks of cardiac irregularity, especially during and after meals, with epigastric distention, oppression, or even pain, a series which, with some degree of arteriosclerosis in radial artery and aorta, may simulate *epigastric angina* very closely." In the latest edition of his manual of pharmacology, Sollmann,³ in discussing the toxicology of caffeine, says "With larger doses, the pulse is full and hard, quickened or slowed, with palpitation and precordial distress (sometimes anginal attacks)." In a recent monograph I have made brief reference to the cardiac pain due to coffee⁴, but most of the newer texts on diseases of the heart fail to mention it, although a number of other toxic effects are noted, particularly premature contractions. In the following two cases, the relationship between the drinking of coffee and the occurrence of pain seemed clearly established.

CASE REPORTS

Case 1 A physician, aged 38 years, was first seen in December 1927. He complained of precordial pain of two months' duration. He had enjoyed excellent general health. He played squash two or three times a week without discomfort. He was working hard and nervously awaiting the birth of a second child. Up to three weeks before his visit, he smoked six or eight pipefuls each day. He rarely took alcohol. He drank two large cups of coffee and two cups of tea daily.

The present illness began two months previously, with an arrhythmia due to premature beats. He stopped smoking on this account. For four weeks he had

* Received for publication July 28, 1937.

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noted pain in the chest, usually precordial, but sometimes substernal. This was not severe, was unrelated to effort and lasted for several hours or even for several days. There was sometimes a sense of heaviness in the left arm. He played squash without aggravating the discomfort. There was no dyspnea. He was much upset because of the possibility that his symptoms indicated the presence of coronary sclerosis.

On examination there were no signs of organic cardiac disease. The heart rate was 60, the rhythm regular. The sounds were normal. The blood pressure was 118 mm Hg systolic, 72 diastolic. The heart was transverse in position, but was not enlarged on roentgen-ray examination. The electrocardiogram showed a moderate degree of left axis deviation, with inversion of the T-wave in Lead III.

He was reassured and advised to stop taking coffee and tea. He was told to resume smoking in moderation and to continue with his usual exercise.

One month later he reported that the pain in the chest had completely disappeared and that a cup of coffee or tea would bring it on as before. Even Sanka induced discomfort. Because he was still somewhat skeptical as to the relationship of coffee to his pain, the following experiment was carried out. At intervals of a week, for four consecutive weeks, he was sent a capsule, the contents of which were not known to him. Two of the capsules contained 0.13 gm (2 grs) of citrated caffeine, the others an equivalent amount of milk sugar. He was able to distinguish between them in each instance, the caffeine precisely reproduced the pain which he had been having, the milk sugar caused no symptoms.

He was seen again seven months after his first visit. He had attempted to take coffee, but found that it again caused pain. Examination was negative, as before.

In November 1932, the patient reported that his sensitiveness to coffee had disappeared and that he could now drink it without subsequent pain.

In March 1937, he reported that he had been drinking coffee during the intervening years without recurrence of cardiac pain. At times, however, about an hour after taking a cup of coffee there was marked sweating of the palms of the hands. He was convinced that coffee caused his original symptoms.

Case 2 A lawyer, aged 40 years, was first seen in December 1930, complaining of precordial pain which had been present, at intervals, for a year. At 18, he had nephritis and was out of school for a year. Subsequent tests of renal function showed a good recovery. He was refused for military service in 1918, because of albuminuria. There had never been hypertension or edema. He took two cups of coffee each day, but no tea. He did not smoke or use alcohol. He was of a worrisome nature and dreaded trial work, which, because of the limited business available, he was obliged to undertake. He had been married 12 years, his wife and two children were living and healthy.

The present illness began the year previously. He was in the habit of playing squash several times a week. Always, after exercise, he noted upper precordial pain, not severe and without radiation. This would usually last for several hours, "it felt as though a muscle had been pulled." There was a tender spot in the region of the third left interspace. The pain never occurred during exercise, but always after it. He could walk briskly for two or three miles, but on sitting down later would have an aching sensation in the precordium for two or three hours. There was no dyspnea. He consulted a physician, who suggested that an electrocardiogram be taken by a diagnostic laboratory. The report stated that the myocardium was severely damaged. He was advised to give up all exercise and to curtail his work. He was naturally greatly distressed.

The patient was a high-strung, introspective man. Physical examination was negative. There was no evidence of arterial or arteriolar sclerosis. The heart rate was 80, the rhythm regular. The sounds were of good quality. The blood pressure was 146 mm Hg systolic, 86 diastolic. There was no enlargement of the heart by orthodiagraphic measurement. The electrocardiogram showed slight notching of the

S-wave in Leads I and II, and of R in Lead III. There was also very slight elevation of the S-T segment in Leads II and III (figure 1). The urine contained a faint trace of albumin, but no casts or blood cells.

The patient was told to resume a normal life, including the playing of squash. He was advised to give up coffee.

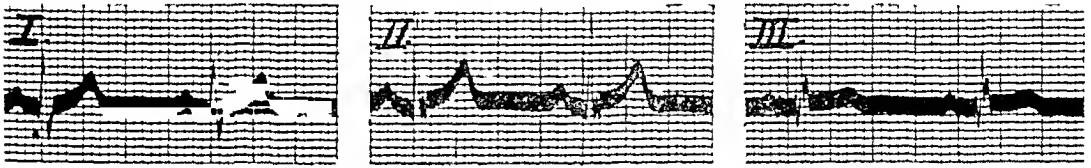


FIG 1 Electrocardiogram of Case 2. For description, see case report in text.

Two months later, he stated that he had an occasional twinge of pain after violent exercise, but this was negligible. He was still working under strain. The blood pressure was 136 mm Hg systolic, 84 diastolic. In April 1934 (four and one-half years after his first visit) he stated that he had never been so well. The cardiac pain had completely disappeared. He was playing squash and working hard.

He was seen again in June 1935. He was much happier and had been very successful as a lawyer. He had given up squash, but played doubles at tennis and walked briskly without discomfort. He again wanted an appraisal of his condition. Examination was essentially as previously described. The electrocardiogram was exactly as it had been on the first examination.

The patient reported by telephone on July 9, 1937. His general health was excellent. There was no recurrence of pain and he felt certain that his original discomfort was due to coffee. He drank Sanka or Kaffee Hag, but had not tried coffee. He continued to play tennis and golf. He was effusive in his gratitude and felt that by giving up the use of coffee and being reassured about his heart, he had been spared a life of invalidism.

COMMENT

These two cases are examples of a small series seen in office practice. They are particularly significant because of the relatively long follow-up periods, namely nine and one-half years in one patient, six and one-half in the other. The experiment with caffeine carried out in the case of the physician demonstrated conclusively that, in this instance, discomfort was due to the caffeine content of the coffee, not to reflex digestive disturbances induced by its volatile, oily constituents. The slight changes in the form of the electrocardiogram in the second case served at first to confuse the clinical picture but proved to be a source of unnecessary concern.

The number of such cases is not large, but, in my experience, cardiac pain due to coffee is more common than that due to tobacco.⁴ Tea, because it is taken weaker and, as a rule, in smaller quantities, is less frequently concerned. This type of pain occurs predominantly in persons with apparently normal hearts, discomfort caused by tobacco is more frequent in patients with diseased coronary arteries who have already experienced spontaneous attacks.

The character of the pain is different from that of the so-called

"anginal" type, in that it is not severe, is of relatively long duration and is not induced by effort or emotion. It may radiate to one or both arms, causing a sensation of heaviness or soreness. When present, it is not aggravated by exercise. The discomfort is not relieved by taking nitroglycerine. Physical examination reveals no signs of organic cardiac disease. In spite of these distinguishing features, mistaken diagnoses have been made and patients have been alarmed and restricted in their activities without good cause.

All of those whom I have seen with pain due to coffee have been high-strung, tense individuals. Several have been under mental and emotional stress, induced by such causes as economic difficulties, marital incompatibility or a heavy load of responsibility. The question may be asked as to whether they were suffering from a psychoneurotic state with cardiac symptoms. This seems unlikely, for the pain disappeared promptly after stopping the use of coffee in each instance. It is more probable that their increased susceptibility to coffee was due, in part, at least, to a lowered nervous threshold. The subsequent history of the physician (Case 1) indicates that this susceptibility may be transitory. The course of these patients has shown that they were not suffering from any serious, organic cardiac disease, coronary sclerosis, if present, has not manifested itself by symptoms or signs. The lawyer (Case 2) has so far enjoyed almost 10 years of active life and has achieved, during this period, conspicuous success in his profession.

The action of caffeine on the heart and blood vessels is both central and peripheral, varying with the amount taken. A cup of coffee or strong tea contains about 0.1 gm ($1\frac{1}{2}$ grs) of the alkaloid. The predominant action of moderate doses consists in vasodilation combined with cardiac stimulation. The heart rate is accelerated, the amplitude of cardiac contractions is increased and cardiac output is correspondingly augmented. In experimental animals, the coronary blood flow is increased. The areas of the brain which control psychic processes and the medullary centers (respiratory, vasomotor, vagus) are stimulated.

The usual effects of poisoning due to coffee are nervousness, palpitation, insomnia, headache and digestive disturbances. In susceptible persons, especially those of "nervous" disposition, these symptoms are exaggerated. Chronic caffeine poisoning causes palpitation which is sometimes associated with a cardiac arrhythmia, most frequently due to premature beats. Dyspnea may occur. Neuralgias of various sorts have also been described.⁵

Brow, Long and Beattie⁶ injected caffeine intravenously into decerebrated cats and produced extrasystoles. This result was obtained after all nerve connections to the heart were severed and the suprarenal glands were removed. They concluded that the site of action of caffeine was either on the myocardium or the sympathetic nerve endings in the heart. Dikshit,⁷ on the other hand, observed that caffeine could produce extrasystoles by an action on the hypothalamic centers.

It appears, then, that caffeine may affect the heart both by its direct effect on the cardiac muscle and nerves, and indirectly through the hypothalamus. The manner in which it causes cardiac pain cannot be explained satisfactorily until more definite information is at hand concerning the mechanisms by which painful stimuli are initiated in the heart. The fact remains that, in certain persons unduly susceptible to caffeine because of increased nervous irritability or for some other unknown reason, coffee may induce cardiac pain. To recognize the existence of this relationship is, on occasion, of practical clinical importance.

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CASE REPORTS

MYXEDEMA AND DIABETES MELLITUS A CASE REPORT WITH AUTOPSY FINDINGS *

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THE patient reported in 1930¹ as having the rare combination of myxedema and diabetes died in November 1936 of carcinoma of the bowel. An autopsy was done and the complete report of the case is herewith presented (summarized in table 2)

The number of cases in the literature is not large. Shepardson and Wever⁹ and Weinstein¹⁰ have recently added to the series and in so doing have sufficiently surveyed the literature and the subject in general. One additional case (Castex et al.) has been reported since their article appeared and a summary of the total series is given in table 1. The autopsy record herewith reported on our case is the second one in the literature, the other being that of a case of Weinstein's

TABLE I

Cases of Spontaneous Myxedema and Diabetes Mellitus

Ewald	1895	Berl klin Wchnschr, 1895, xxvii, 25
†Gordon	1904 (2)	Am Med, 1904, vii, 299
Shasser	1905	Jr Am Med Assoc, 1905, xlii, 765
†Holst	1923	Schweiz med Wchnschr, 1923, iv, 725
Brown	1924	Lancet, 1924, i, 59
†Wright	1926 (2)	Clifton Med Bull, 1926, xii, 88
Wilder	1926	Arch Int Med, 1926, xxxviii, 736
Jamieson	1927	Canad Med Assoc Jr, 1927, xvi, 88
Carey	1930 (1)	Minn Med, 1930, xiii, 578
Carey	1926	Same case with autopsy herewith reported
Weinstein	1932 (2)	One autopsy—Johns Hopkins Hosp Bull, 1932, li, 27
Daniels	1932	Nederl tijdschr v Geneesk, 1932, lxxvi, 1555
†Joslin	1928 (3)	The treatment of diabetes mellitus, Lea and Febiger, 1928, p 890
Joslin	1933	Quoted by Shepardson and Wever
Shepardson and Wever	1933	Internat Clin, 1934, iv, 132
†Rohdenberg	1922	One case with autopsy, Endocrinology, 1922, vi, 519
Castex, M R, Schein- gart M, Mollard H	1933	Rev Sud Am de Med et de Chir, 1933 iv 1

* Received for publication February 15, 1937

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† The cases reported by Gordon, Holst, Wright, Rohdenberg and one of Joslin's in 1928 are open to some question, that of Holst for instance was postoperative myxedema, not spontaneous, Gordon's cases were not well studied as to basal metabolic rate, and Wright's cases may have been only hypothyroid, although they seemed to have some of the symptoms of myxedema. One of Joslin's cases is of this same character, and in Rohdenberg's case the "diabetes" had disappeared before the onset of the myxedema. An autopsy done in this latter case showed atrophy of thyroid and hypertrophy of islands of Langerhans of the pancreas, but detailed studies of neither metabolic conditions were made during life

TABLE II

Date	Basal Meta- bolic Rate Per Cent	Weight Kg	Blood Sugar Per Cent	24-hour Urine Sugar Grams	Thyroid Sub- stance Per Day Grams	Units In- sulin Per Day	Diet
6-29-21	-36	75.8	—	—	6	—	This diet continued all during this period as well as his wife could manage it. It certainly was not accurately maintained.
10-3-21	-6	66.0	—	—	4-6	—	
4-3-22	+2	76.4	—	—	4-6	—	
8-28-28	-17	70.0	174	—	4	15	
9-1-28	—	—	—	33	2	30	
9-14-28	+27	66.0	—	4	2	30	
10-5-28	—	—	—	3	2	30	
10-18-28	+7	69.0	—	—	2	30	
12-20-28	+12	67.0	—	13	2	30	
7-17-29	+1	58.0	285	—	2	30	
3-31-30	+11	60.0	222	—	2	30	Carbohydrate 110
4-4-30	—	—	—	8	2	35	Protein 70
11-14-30	+2	60.0	384	10.5	2	45	Fat 180
12-3-30	—	—	—	reduction	2	40	
12-18-30	—	—	—	none	0	36	
1-8-31	—	—	—	none	0	30	
1-17-31	—	—	—	+qualitative	2	28	
2-16-31	—	—	—	+qualitative	2	31	
2-19-31	+6	60.0	384	22.8	2	31	
3-7-31	—	—	—	4.2	1	36	
9-11-31	—	—	444	31.2	1	36	
12-2-31	+3	73.0	377	8.2	1	33	
4-14-32	—	74.0	—	2.4	$\frac{1}{2}$	33	
5-17-33	-1	75.0	449	—	1	36	
1-5-34	+2	69.0	654	28.2	1	57	

CASE REPORT

A W S, male, aged 44 years, appeared for examination June 28, 1921, complaining of weakness, aching legs and shortness of breath. He stated that in March 1920 he began to feel general malaise, was easily fatigued and had some aching of legs and dyspnea on exertion. He had been treated for pyorrhea at that time without relief of symptoms. Upon questioning, it was brought out that he had suffered from impairment of visual acuity, his mental processes were considerably retarded, and his hearing especially had become quite poor. He found it almost impossible to keep awake and would usually fall asleep anywhere if he remained in a sitting position for any length of time. He had gradually gained in weight and his flesh had become soft. He had become stooped and "round shouldered" during the past year and had experienced great difficulty in holding his head erect. His hair had become dry and had fallen out, his skin was dry, although he perspired readily. There had been some swelling of the legs from the knees down, which did not vary greatly on change of posture. His wife further stated that his pulse had become slow, being about 50 when she had counted it. The family and past history were unimportant. He had two children and his wife had had two miscarriages, both at about six weeks.

Examination revealed a dry, scaling skin, thin dry hair and scaly scalp. The face was puffy especially around the eyes, and the color was rather pale. General musculature was flabby with an increase of fat deposit at the back of the neck and on the abdomen. The pulse was slow (50 to 56), full in volume but of low tension. Respiration was also slow. As the individual was questioned, his attention wandered, his speech was slow and thick and his answers were often inaccurate when checked.

by his wife. The eyes were negative except for a drooping of the upper lids. The examination as to heart, lungs and abdomen was entirely negative. The reflexes in the extremities were sluggish. There was no true edema but a typical myxedematous palpatory sensation of the subcutaneous tissue was present. The first blood pressure reading was 108 systolic and 80 diastolic. Important laboratory findings at this original examination were: Negative urine tests, a negative blood Wassermann and a basal metabolic rate of minus 36 per cent. He was placed on 6 gr. of desiccated thyroid substance daily and his subsequent course can be readily seen by reference to table 2. There was the expected symptomatic improvement and from 1922 to 1928 he was not seen, although we corresponded with him at intervals.

During the winter of 1927 he developed symptoms of diabetes, that is, he lost weight rapidly, had great hunger, thirst and weakness. The doctor in the town to which he had moved found sugar in his urine. There was great difficulty in establishing a proper balance between diet, glycosuria and thyroid dosage. Finally in August of 1928 he returned to the clinic for examination and management. At this time he was found to be thinner than before and without any signs or symptoms which one could identify as being myxedematous except that his pulse rate was slow and his basal metabolic rate was minus 17 per cent. The blood pressure at this time was 120 systolic and 80 diastolic. Again his course can best be followed by reference to table 2.

The patient was not very cooperative, insisting upon an adequate daily food intake in order to do his work as janitor. He would not report at regular intervals for checking up but usually came when either he or his wife was worried about something.

We tried to eliminate the thyroid substance, thinking that perhaps the diabetes might be better controlled if we allowed the basal metabolic rate to drop to 10 or 15 below normal. The patient, however, had a great fear of relapsing into his previous lethargic state and insisted upon taking a small daily dose of thyroid substance. During the time when he was first found to have diabetes he had a few unfortunate insulin reactions and had developed some fear of an over-dosage of it. Perhaps due to the peculiar combination of things in this case these personal factors are not very important, but they are recorded as a possible explanation for the difficulty in controlling the diabetic factor. If the basal metabolic rate had been allowed to drop below normal, and if the patient would have consented to either limiting his food intake or increasing his insulin dosage, perhaps the balance could have been better maintained.

He was, however, checked at intervals with results recorded upon the accompanying chart. It will be noted that his weight fluctuated slightly, and that his fasting blood sugar tended to remain at a higher level from 1930 on. The insulin dosage was varied from time to time by his wife, according to her ideas of his needs based upon an occasional examination of urine with Benedict's solution and the occurrence of mild insulin reactions. He complained frequently of cramping pain in his legs. His blood pressure on March 31, 1930, was 132 systolic and 78 diastolic and an electrocardiogram was normal in all leads (figure 1).

In September 1931 he suffered from an infection of the leg resulting from a varicose ulcer. During this time his wife reported the occurrence of much more sugar in the urine, so instead of modifying his diabetic program she eliminated the thyroid entirely until the infection healed—a period of about six weeks.

In December 1933 he became careless with his diet and his attending physician had to rescue him from an impending coma by the use of 200 units of insulin over a 24-hour period. Shortly after this he came to the clinic for examination, which resulted in the data noted under date of January 5, 1934 (table 2). In addition to these findings his sugar and insulin tolerance were studied by making blood sugar deter-

minations throughout the day on his regular routine The results of this study were as follows

9 30 a m Fasting blood sugar 654 mg per cent
20 units insulin administered and breakfast of approximately 24 gm protein, 47 gm fat and 78 gm carbohydrates

11 00 a m Blood sugar 562 mg per cent
11 30 a m Blood sugar 526 mg per cent
12 30 a m Blood sugar 421 mg per cent
20 units of insulin administered and lunch of approximately 26 gm protein, 42 gm fat and 18 gm carbohydrates

3 00 p m Blood sugar 171 mg per cent
4 30 p m Blood sugar 75 mg per cent

At this reading a feeling of weakness, some sweating and slight tremor were noted, so he ate his supper early and returned home

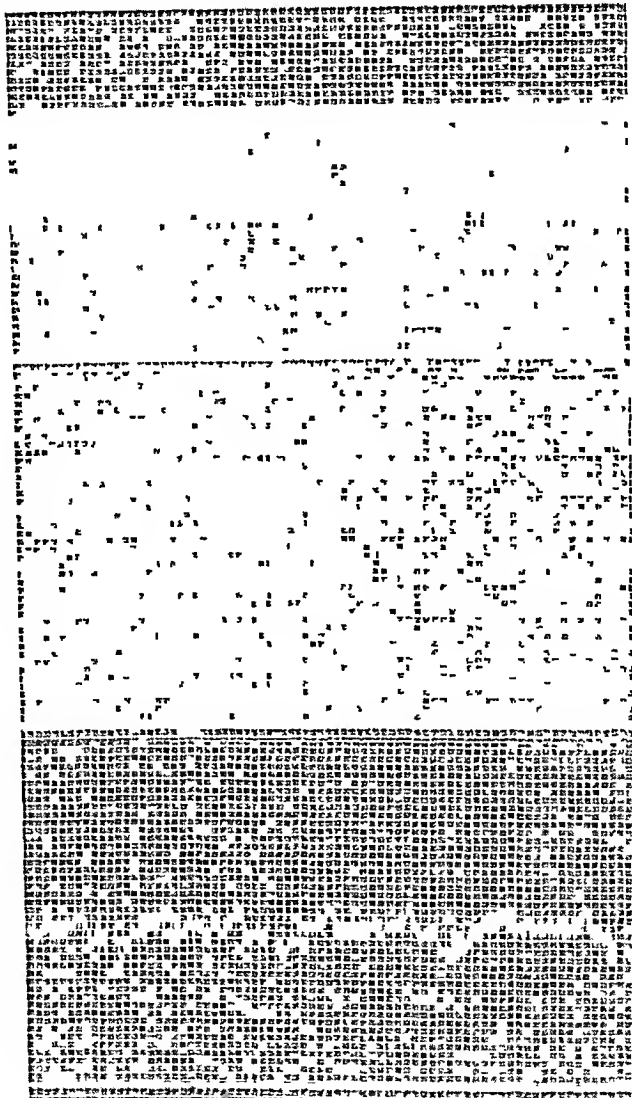


Fig 1 Normal electrocardiogram (see text)

He was advised to discontinue his daily grain of thyroid, to adhere more strictly to his diet (which he still insisted must be adequate and which was of the approximate values shown on the chart), and to use insulin units 40-10-5 daily

On July 22, 1935, he was brought into the hospital with a greatly distended abdomen. His bowels had not moved for several days and intestinal obstruction was suspected. His urine showed four plus sugar, acetone and diacetic acid. His breath was acidotic and his blood sugar was 770 mg per cent. He was given 140 units of insulin with glucose together with colon irrigation, and over a period of 48 hours his acidosis cleared up and his urine became sugar free and also the supposed bowel obstruction was apparently relieved. At least the enemata brought away large amounts of fecal material and gas and the abdominal distention decreased. Previous to this he had been using about 45 units of insulin daily. He was discharged from the hospital without further bowel study and returned to his former program of diet, insulin and thyroid daily. His attending physician reported that from that time until the final events he had several attacks of abdominal distention relieved by enemata. After each such incident, however, his abdomen remained somewhat more distended than before. His bowels were usually constipated but with occasional attacks of diarrhea. The most violent of these attacks were in February and July 1936 and these were accompanied by coma. There was no vomiting at any time and very little pain. Finally about November 10, 1936, he showed signs of obstruction with enormous abdominal distention, this time not relieved by enemata or abdominal stupes. He became progressively weaker and finally died November 16, 1936. The autopsy was performed within five hours of death by Dr E H Norris, whose record of the autopsy is as follows

"The body is that of a well-developed white man, 185 cm long, weighing about 170 lbs. The face, shoulders, arms, forearms and hands are extremely emaciated. The veins of the arms and shoulder regions stand out prominently. There is huge distention of the abdomen, the highest point above the table being 38 cm. There is marked edema of the lower extremities below Poupart's ligaments, a bit more marked on the left than on the right. There is tremendous edema of the scrotum and penis. Rigor is not present. Hypostasis is evident over the posterior parts, no cyanosis or jaundice. The pupils are 6 mm in diameter.

"Upon incising the skin of the abdomen the edges retract spontaneously so that they are separated by a distance of 15 cm before the peritoneum was incised. The peritoneal cavity contains about 500 c c of clear straw-colored fluid. The diaphragm reaches the third interspace on the right, the fourth rib on the left. The colon is hugely dilated from a point about 30 cm proximal to the anus, where a firm small annular carcinoma apparently occludes the bowel. The dilated portion of the colon measures 42 cm in circumference, the entire length of the colon, including the portion distal to the carcinoma, is 200 cm. There is moderate edema and slight dilatation of the lowest portion of the ileum. A large Meckel's diverticulum is present. The appendix is atrophic and presents as a white cord.

"The left pleural cavity has no adhesions, contains 200 c c of clear fluid. The right cavity is obliterated by firm adhesions. The pericardial sac contains about 40 c c of clear fluid and no adhesions.

"The heart weighs 250 grams. There is one white soldier spot on the left ventricle. There is no lesion on the valvular or mural endocardium. The musculature is of normal consistence, brown in color and shows no gross fibrosis. The coronary vessels are patent at their orifices, along their trunks they show grade I atherosclerosis with some thickening and slight narrowing of the lumina.

"The right lung weighs 400 grams, the left 220 grams. There is crepitation throughout both lungs but slightly diminished in both. The cut surfaces yield almost no fluid and no pus. The lungs appear drier than normal.

"The spleen weighs 75 grams. Its capsule is wrinkled. The pulp appears

fibrous and a number of small white nodules are scattered through it. The nodules vary from 2 to 6 mm in diameter.

"The liver weighs 1300 grams. The capsule is smooth. Two areas of infiltrating tumor are seen through the capsule. On section several other white areas of infiltration are noted. These metastatic lesions are not large or extensive, the largest is about 5 cm in diameter. The parenchyma of the liver is lighter in color than normal. A yellow cast is apparent and the general tone might be described as dark tan. The lobular markings are not clearly recognizable. The gall-bladder is markedly distended with thin dark bile, no concretions.

"The stomach, duodenum and small intestine are essentially normal, except as noted above. There is a small firm polypoid nodule projecting from the surface of the stomach about 1 cm proximal to the pyloric ring.

"The pancreas weighs 55 grams. It is small and atrophic, the atrophy seems to be general but perhaps is most marked in the head portion. Microscopically the acinous and islet tissues appear normal morphologically. There is no increase in the fibrous stroma. The impression is strong, however, that there may be fewer islands in the tail region of the gland than is normal. The right adrenal weighs 6 grams, the left 6.5 grams. They appear normal.

"The right kidney weighs 130 grams, the left 160 grams. The capsules strip with ease, leaving smooth surfaces. The cut surfaces show no lesions. There is moderate dilatation of the right ureter, extending from the bladder to the region of the pelvic brim. The bladder shows no gross lesion. The prostate is small. The seminal vesicles, epididymides and testes show no gross lesions.

"The root of the aorta and the thoracic and abdominal portions show grade I atherosclerosis. A number of raised oval plaques are noted but there is no ulceration and no evident calcification.



FIG 2 Microscopic section of thyroid gland (See text for description)

"The organs of the neck are studied after removal of the larynx. The thyroid gland is scarcely recognizable, no normal thyroid tissue is apparent. The organ can be identified by the form and distribution of such tissue as is present, which is yel-

lowish white, very soft and flabby Both lateral lobes, the isthmus and the pyramidal lobe can be recognized after careful dissection The microscopic findings of the sections of the thyroid gland tissue showed almost complete replacement of the follicular parenchyma by collagenous fibrous tissue In a few scattered areas greatly distorted epithelial structures can be found (Figure 2) Four parathyroids are recovered and appear to be normal

"The lymph nodes of the mesentery and those around the celiac axis and pancreas are bright yellow and soft The reticulo-endothelial cells of the mesenteric nodes show large amounts of neutral fat and lipoids The hilar nodes in the mediastinum are anthracotic and contain similar tissue, no other change

"The brain shows no gross lesion The vessels at the base show no sclerosis The hypophysis and pineal gland are grossly normal

"There is only a very small amount of fat present in the subcutaneous tissue, in the mesentery and in other parts where fat might normally be found

Diagnoses 1 Atrophy of the thyroid and pancreas 2 Huge megacolon 3 Carcinoma of the sigmoid with metastases to the liver 4 Myxedema (clinical) 5 Diabetes mellitus (clinical) "

A complete discussion of the various aspects of this association of myxedema and diabetes will be found in the papers of Shepardson and Wever,⁹ Weinstein¹⁰ and of one of us¹ Others^{11, 6, 2, 5, 3, 7, 4, 8} have also commented upon the effect of hyper- and hypothyroid states on carbohydrate metabolism Although the occurrence of myxedema and diabetes in the same patient is probably wholly fortuitous, there seems to be no doubt that, once established, there is a reciprocal reaction of the secretions of the two glands concerned It is not apparent that the diabetes influences the myxedema, but it is certainly evident that the myxedema modifies the diabetes That is, whenever the metabolic rate is increased by the administration of thyroid, the carbohydrate tolerance is markedly reduced In spite of this, of the two recorded deaths neither was due to either diabetes or to the effects of myxedema In Weinstein's case death was said to be due to heart failure of congestive type, and at post mortem high grade arteriosclerotic aortic valvular disease was found—apparently not a myxedema heart, although no other details of the pathological examinations of the cardiovascular system were given Our case died of intestinal obstruction

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COARCTATION OF THE AORTA, DISSECTING ANEURYSM, AND ANEURYSMAL DILATATION OF THE LEFT VERTEBRAL ARTERY, REPORT OF A CASE*

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ALTHOUGH several unusual, indeed, almost unique features alone justify the publication of this case, a more compelling motive, the equally rare correct appraisal of the situation, is responsible. Only 10 per cent of the cases of aortic coarctation have been recognized ante mortem and its discovery at postmortem examination remains a "surprise d'amphitheatre". One of us (L J B) has had the opportunity to make the presumptive diagnosis of coarctation of the aorta twice within two years on the basis of hypertension, marked differences in the blood pressures in the arms and legs, notching of the lower borders of the ribs and absence of the aortic arc with dilatation of the ascending aorta. However, the coarctation was completely unsuspected in the present case.

The same general situation prevails in respect to dissecting aneurysm. Less than 5 per cent of the reported cases have been recognized ante mortem. The typical features of this case permitted belated but ante mortem recognition. The combination of coarctation of the aorta and rupture (or dissecting aneurysm) is evident in 16 per cent of the cases of isthmus stenosis reported in the literature.

Since the circulation for the lower half of the body is derived almost entirely from the subclavians in aortic coarctation, it is not surprising that the vertebral arteries, representing the first subclavian branches and participating in the formation of collateral circulation, should become elongated and dilated. However, distinct aneurysmal dilatation of one vertebral artery, sufficient to induce partial pressure atrophy of the cerebellum, as occurred in this case, is extremely unusual. While this dilatation probably represented an associated vascular anomaly, it did not occur at the bifurcation of a vessel and did not represent a "congenital military aneurysm" whose rupture accounts for the hemiplegia.

A brief résumé of the significant points follows.

CASE REPORT

A C, a 57 year old housewife, entered the Metropolitan Hospital October 8, 1936, at 8 30 p m, complaining of weakness and of very intense pain in the right abdomen and right kidney region.

* Received for publication December 30, 1936.

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Four years before she had experienced a very severe epistaxis. At that time her physician discovered hypertension. Dyspnea on exertion, edema of the ankles at night, and nocturia two to three times have been noted during the last two years. Menopause occurred 13 years ago, venereal infections were denied. No pregnancies.

One week prior to admission while doing housework, she was suddenly seized with excruciating pain in the right lumbar region. This pain radiated downwards. At the same time she noted severe precordial pain, a choking sensation in the neck, and these were accompanied by vomiting. In a few hours the choking sensation and vomiting ceased but the pain and weakness persisted. She applied mustard plasters to the back and chest for the relief of pain but without success.

Examination The patient was a well developed obese white female lying in bed apparently in pain. Slight cyanosis of the lips and tip of the nose was observed. Neither dyspnea nor orthopnea was evident. Over the left lower anterior chest and over the entire lumbar region there was a large first degree burn (mustard plasters).

Head No scars, deformities, nor abnormalities. *Eyes* Pupils equal and react to light and accommodation. No nystagmus, strabismus nor disturbance of extraocular muscle movements. The arteries of the fundi are sclerotic, but no hemorrhages are present. *Nose* Septum deviated to the right. Mucous membranes normal. *Mouth* Teeth stained and carious, tongue coated, throat moderately injected.

Chest Breasts large and pendulous but no masses. Chest expansion free and equal, no abnormal pulsations, lungs negative. *Heart* PMI in the sixth interspace at the anterior axillary line. No murmurs or thrills elicited. The aortic second sound was accentuated. The cardiac rhythm was regular, rate 100. The heart sounds were distant. The radial pulses were equal, synchronous, and regular, blood pressure 180 systolic and 120 diastolic in both arms.

Abdomen No viscera could be palpated and there was no evidence of free fluid. No tenderness, rigidity or masses. *Back* Marked tenderness in both lumbar regions, otherwise negative.

Extremities No edema or clubbing, the normal reflexes were present and no pathological reflexes could be elicited.

Impression On admission she was regarded as an instance of hypertensive cardiovascular renal disease developing upon an arteriosclerotic basis with probable renal arteriolar sclerosis. It was thought that she should be regarded as a hypertensive angina pectoris rather than a coronary infarction in view of the maintenance of the high blood pressure level. Lumbar radiation of pain in coronary infarction has not been encountered by the writers and suggested a renal lesion, possibly nephrolithiasis. As liberal amounts of morphine scarcely blunted the pain it was decided to defer further investigation until the patient was more comfortable.

Throughout the following day the pain was less severe. Blood chemical tests were normal. The blood Wassermann test was three plus. The white blood cell count was 13,200 with 80 per cent polymorphonuclears. In view of the evident improvement it seemed advisable to postpone electrocardiographic examination.

At 8 00 p.m. that night she again complained severely of intense aching pain in the lumbar region and severe aching pain in both sides of the chest. The blood pressures remained unchanged. At 11 00 p.m. the patient became stuporous and was unable to speak. There was constant moaning, and rubbing of the lumbar region with her right hand. Respirations were rapid and shallow. The face was pale and the body covered with cold sweat. Soon there appeared a complete paralysis of the left arm, leg, and face. The pupils were equal but the right reacted poorly to light. Within a few minutes no pulse could be felt at the left wrist and no blood pressure could be obtained in this arm. The blood pressure on the right arm was now 200 systolic and 75 diastolic and the pulse was full and regular. On the basis of the

symptomatology now present a presumptive diagnosis of dissecting aneurysm was suggested (Dr Carl Nussbaum) At 12 30 p m she had a generalized convulsion and died

An abbreviated account of the post mortem follows (courtesy of Dr Andrea Saccone)

The body is that of a well developed white adult female Rigor mortis is complete, livor mortis present posteriorly The hair is grey The pupils are equal, regular and in mid-dilatation Lips, finger tips and toes are cyanotic A large erythematous area is noted over the entire lumbar region

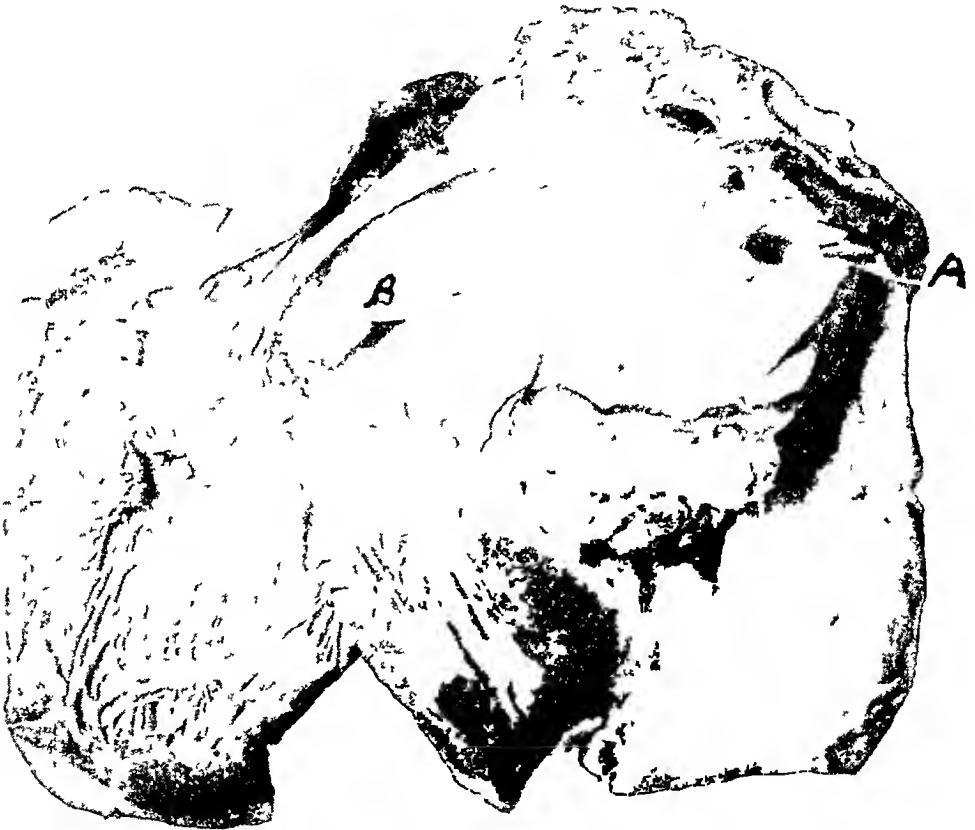


FIG 1 The coarctation may be seen at the upper right of the illustration (A) The large vessels of the arch, normal in number and arrangement but enlarged owing to their participation in the formation of anastomoses, are evident just to the left of the coarctation The atheromatous patches in the intima can also be identified Proceeding to the left is the longitudinal tear in the aorta (B), below this, two of the aortic cusps are visible (This illustration became available through the courtesy of the Medical Examiner's Office, New York City The specimen has been placed in the museum of that department)

On mid-section the subcutaneous fat measures $1\frac{1}{2}$ cm in thickness There is no free fluid either in the abdominal or pleural cavities The pericardium contains 300 c c of blood, most of which is clotted and envelops the heart

The epicardium is infiltrated with a moderate amount of fat The coronary vessels are tortuous The right heart is soft, the left firm The muscle of the right

ventricle measures 3 mm in diameter while that of the left ventricle is $1\frac{1}{2}$ cm in thickness. There is some hardness at the base of the aortic valve but its cusps are normal in number, size and arrangement. The orifices of the coronary vessels are normal. About 2.5 cm above the line of closure of the aortic valves there is a longitudinal tear in the intrapericardial portion of the ascending aorta. This tear extends through the aorta and is the source of the blood in the pericardial cavity. The entire aorta, the branches of the arch and both iliac arteries have been dissected by a large accumulation of blood between the intima (?) and media. The innominate, carotid and left subclavian are very large and branches of the left subclavian are particularly enlarged and show well developed anastomoses. No anomalous branches from the aorta were noted. The intima is covered by many scattered atheromatous patches. At the isthmus of the aorta, just at the ligamentum arteriosus, there is a decided narrowing of the lumen by a firm ring-like thickening so that the lumen of the aorta at this point will just admit a lead pencil. The diameter of the aorta above the coarctation is considerably greater than the diameter below. The mitral and tricuspid valves are normal. Both auricular appendages are clear. The myocardium is uniformly dull brown in color.

The right lung is soft in consistency and dark in color. On section some bloody fluid oozes from the cut surface. The left lung is similar. The gall-bladder is filled with a small amount of thin bile. The liver cuts easily and shows a moderate nutmeg appearance. The splenic capsule is wrinkled and the pulp soft. The pancreatic parenchyma shows congestion. The duodenum is edematous and the remainder of the intestine reveals congestion. The adrenals are separated into two layers by edematous hemorrhagic fluid. The kidney capsule strips easily leaving a granular surface with prominence of the stellate veins. The markings are lost. The cortex is narrow and irregular and the entire parenchyma markedly congested. Uterus and adnexa are normal. The bladder mucosa is congested.

Some thickening of the bone is noted upon removal of the calvarium. The dura as well as the leptomeninges is markedly congested. There is moderate cloudiness of the sulci. The left vertebral artery is markedly dilated and tortuous and forms a short fusiform dilatation, $1\frac{1}{2}$ cm in diameter. The inferior surface of the left cerebellar hemisphere is correspondingly indented by the dilatation of this vessel. The cerebellum is asymmetric and the right vertebral artery is thinner than the left. The left lateral ventricle is slightly enlarged, no change at the base of the fourth ventricle or in pons. The remainder of the brain reveals a lacunar stage of cerebral arteriosclerosis with lesions located principally in the gray nuclei of the right hemisphere.

Anatomical Diagnosis Hemopericardium, rupture of the aorta, dissecting aneurysm of the aorta, branches of the arch and iliac arteries, coarctation of the aorta, fusiform dilatation of the terminal portion of the left vertebral artery, generalized arteriosclerosis, pressure atrophy of the inferior surface of the left cerebellar hemisphere, passive congestion of the lungs, cloudy swelling of the liver, passive congestion of the spleen, chronic diffuse nephritis with terminal congestion, congestion of brain.

Upon microscopic examination of the aorta with special reference to the vasa vasorum no evidence of syphilis or other lesion could be found. The intima was dissected and degenerated near the tear with an adherent clot of fibrin, elsewhere it is thrown into irregular folds. Near the tear the elastic membrane is completely torn and there is a faint necrosis of the media which elsewhere merely shows dissection. The adventitia is negative. Examination of the kidney sections shows a chronic glomerular nephritis with terminal nephrosis.

COMMENT

If coarctation of the aorta had been suspected it is probable that a marked difference in the blood pressures of the arms and leg would have been found. However, less than 3 per cent of the reported instances of coarctation, in itself an uncommon anomaly, have been found in females over 50 years of age. Apparently the oldest age of rupture of the aorta associated with coarctation in a female hitherto reported was thirty. Moreover if persistent differences in the arm blood pressures had been found early in this case, we would have been inclined to attribute them to a specific mesaortitis.

Inexplicable hypertension in youths is extremely suggestive of coarctation, apparently this possibility must be considered, even if rarely, in older individuals. It is often stated that glomerular nephritis must be eliminated as a cause of hypertension in suspected coarctation, in this case both lesions existed. If the dissection of the renal arteries and a more protracted course had permitted, uremia might have further complicated the puzzling picture.

Among the signs commonly attributed to coarctation the following were absent in this case: disproportion in size, color, and temperature between the upper and lower half of the body, abnormal pulsations in the neck, back and intercostal vessels, palpable intercostal arteries, parasternal post-systolic murmur. Notching of the lower border of the ribs was not studied by roentgen-ray, but none was found at post mortem. The intercostal vessels did not play an important rôle in the anastomosis. Dilatation of the ascending portion of the aorta would have been found on roentgen-ray but we would probably have attributed it to a non-existent luetic aortitis. Absence of the aortic arc in the second left oblique position ought to have been present. Other signs such as retardation or diminution of the femoral pulse, small oscillometric waves, increased reactive hyperemia in the poorly circulated extremities, the low fall and later, long duration of increased superficial temperature during and after obstruction to the circulation, the long duration of the fall of blood pressure in the lower limbs after application of obstruction to circulation in the upper half of the body would have been equivocal in the presence of dissecting aneurysm.

In retrospect our diagnostic failure may be assigned chiefly to two prevalent mistakes. Our neglect to determine blood pressures in the upper and lower extremities routinely in cases of hypertension, our failure to think of the possible presence of an unusual lesion.

The symptomatology of the dissecting aneurysm in this case was typical. The immediate onset of maximum and severe pain, its unusual radiation (or localization) to below the mid-lumbar region, the nausea and vomiting (aortic depressor nerve?), the maintenance of the high level of blood pressure with regular scarcely elevated heart rate, the development of hemiplegia and the absence of pulse in one arm may be mentioned in passing. The persistent and recurring back pain may be attributed to marked dissection of the intercostal arteries. Supra-pubic cyanosis, said to be present in aortic obstruction at the bifurcation and arising from a "rider" embolus, was absent.

Hemiplegia occurs not infrequently in coarctation of the aorta as the result of cerebral hemorrhage. This may be due to rupture of an intracranial "congenital aneurysm." In this case the hemiplegia may be attributed partly to the occlusion of one carotid artery by the dissection of its walls, partly to the cerebral

edema. Partial or complete disappearance of the carotid pulsation ought to have been elicited in this case but on this point the record is silent.

A careful study of the vasa vasorum failed to reveal any evidence tending to incriminate syphilis as a factor in producing the dissecting aneurysm. Nevertheless it may have facilitated the evolution of the catastrophe. Evidence was also lacking of a *mesaortitis dissecans* in the sense of Babes and Mironescu. The medial changes of Gsell and Erdheim's *medionecrosis aortae idiopathica cystica* were likewise absent. The minute hemorrhages from the vasa vasorum and small mural hematoma described by Moriani were not present. The thinned and faintly staining media together with the fragmented and broken elastic membrane are consistent with the mechanically conditioned transformation of the aortic wall in the presence of persistent hypertension (as described by Einhauser). It does not seem logical to speak of a constitutionally weak aorta when it resisted the onslaught of hypertension for more than one half a century. It is of interest to note that the aortic tear occurred at Oppenheim's point of maximum functional strain of the aorta. In contrast to most cases the tear was longitudinal rather than transverse. This is alleged to facilitate hemopericardium rather than extensive dissection. The presence of concomitant vascular anomalies of constitutional origin is strongly suggested by the aneurysmal dilatation of *one* vertebral artery.

Finally increasingly distant heart sounds with maintenance of the blood pressure in a case of dissecting aneurysm (or coarctation) should justify the diagnosis of hemopericardium even in the absence of increased cardiac dullness. The absence of cardiac hypertrophy and dilatation in the presence of prolonged hypertension, as in this case, should be provocative of thought.

SUMMARY

A case of the adult type of coarctation of the aorta, dissecting aneurysm and fusiform dilatation of the left vertebral artery is presented. Attention is directed to our failure to recognize the coarctation rather than our success in appraising the dissecting aneurysm. Diagnostic errors occur in both lesions with disturbing frequency which may be diminished by popularizing consideration of these lesions as diagnostic possibilities.

EDITORIAL

THE VALUE TO CLINICAL MEDICINE OF EXPERIMENTAL STUDIES ON THE LIVER

It is difficult for the clinician interested in hepatic disease to overestimate the debt owing to laboratory workers who have so diligently studied the pathologic physiology of the liver. Clinical knowledge of hepatic disease, having been almost at a standstill for fifty years, is now being immensely enriched by the contributions of physiologists and biological chemists who have, first, fully informed us of the functions of the liver and later demonstrated its reparative and regenerative properties, its extraordinary reserve functional capacity and, most recently, the activities of the organ in maintaining normal internal environment.

A large part of the success attained by the physiologists has been attributable to their ability to reproduce in the experimental animal two of the common clinical affections, obstructive jaundice and parenchymatous injury. The pathology and physiology of the former condition, easily produced by ligation of the bile ducts, has now been thoroughly studied from its inception to its end stage of obstructive biliary cirrhosis. The simulation of parenchymatous lesions has been a more difficult matter but it is now possible to reproduce an almost perfect experimental counterpart of atrophic cirrhosis by the continued administration of carbon tetrachloride. The effects of variations in the diet on the course of experimental hepatic disease, and on the ability of the liver to repair itself and regain its function after an almost lethal injury have been fully demonstrated by this means.

The protective effect of high carbohydrate diets in poisoning from chloroform and phosphorus, first shown years ago by Opie and Alford,¹ is now known to be equally effective in retarding the development of hepatic damage induced by biliary obstruction and carbon tetrachloride. Diets of high fat content recently have been shown by Bollman² to have an opposite effect. For instance, it is virtually impossible to produce any significant hepatic lesion in the dog by administration of alcohol if the animal is on a mixed diet, with a high fat diet marked fatty degeneration can be produced by this means. Such a diet given alone, without any hepatotoxic agent, also will lead eventually to fatty metamorphosis. Such fatty livers are easily injured by any hepatic poison and undergo necrosis and parenchymatous degeneration even with minimal insults. The only known means of protection against the fatty change produced by dietary means and by certain specific poisons are three: an increased intake of carbohydrate, the adminis-

¹ OPIE, E. L., and ALFORD, L. B. The influence of diet upon necrosis caused by hepatic and renal poisons. I. Diet and the hepatic lesions of chloroform, phosphorus, or alcohol, *Jr. Exper. Med.*, 1915, **XXI**, 1-20.

² BOLLMAN, J. L., and MANN, F. C. The physiology of the impaired liver, *Ergebn. d. Physiol.*, 1936, **XXVIII**, 445-492.

tration of lecithin or one of its components, choline, and the use of a pancreatic hormone designated as "lipocair" by its discoverer, Dragstedt³ and his associates

The relation of the last two mentioned substances to fatty change in the liver is an interesting chapter in itself. The development of hepatic insufficiency in pancreatectomized dogs whose diabetes was controlled by insulin led to an investigation of the morphology of the liver, it was first shown by MacLeod and his collaborators⁴ and later by Best, Ferguson and Hershey⁵ that the underlying lesion was marked fatty degeneration. Similar changes in the hepatic parenchyma are known to occur in the diabetic human subject⁶ and in patients with pancreatic atrophy produced by lithiasis. In the pancreatectomized dog, lecithin or choline has been shown to exert an inhibitory effect on this process, recently Dragstedt and his associates³ have shown that it is possible to extract from the pancreas a hormonal substance which inhibits deposition of fat in the liver after pancreatectomy. This preparation has been used effectively in treatment of one human subject with pancreatic stone and a presumably fatty liver and may have some further clinical application in severe diabetes and in acute fatty infiltration of the liver produced by poisons.

Do these fatty changes constitute the forerunners of nodular cirrhosis? Ordinarily they do not lead to any permanent hepatic lesion in the experimental animal but knowing the extreme vulnerability of the fatty liver, it is reasonable to assume that any added toxic factor might easily lead to the development of parenchymatous degeneration and nodular hyperplasia. It is clear that more attention will have to be paid to the relation of the diet to hepatic disease and that regulation of its fat and lecithin content may well find a place in the therapeutics of hepatic disease.

From the chemical and physiologic laboratories some light has been cast in recent years on the mechanisms by which ascites is produced. It has been demonstrated that the condition does not depend on portal back pressure alone, although in most hepatic diseases associated with ascites there are gross evidences of interference with portal blood flow. Ascites sometimes appears spontaneously as a terminal development in the animal with long-continued experimental biliary obstruction and in such animals may be induced almost at will by oral administration of meat extractives which are virtually free of protein. The same situation exists in animals with cirrhosis induced by carbon tetrachloride but in neither instance is there any satisfactory explanation of why these innocuous meat extracts have this puzzling effect. The spontaneous appearance of fluid, on the other hand, is

³ DRAGSTEDT, L. R., VAN PROHASKA, JOHN, and HARM, H. P. Observations on a substance in the pancreas (a fat metabolizing hormone) which permits survival and prevents liver changes in depancreatized dogs, *Am Jr Physiol*, 1936, cxxvii, 175-181.

⁴ ALLAN, F. N., BOWIE, D. J., MACLEOD, J. J. R., and ROBINSON, W. L. Behavior of depancreatized dogs kept alive with insulin, *Brit Jr Exper Path*, 1924, v, 75-83.

⁵ BEST, C. H., FERGUSON, G. C., and HERSHEY, J. M. Choline and liver fat in diabetic dogs, *Jr Physiol*, 1933, lxxix, 94-102.

⁶ ROOT, H. F. Diabetic coma and acute pancreatitis with fatty livers, *Jr Am Med Assoc*, 1937, cviii, 777-780.

thought to depend on at least three factors, the degree of parenchymatous hepatic injury, interference with portal circulation and reduction of plasma proteins. A slight but progressive fall in concentration of these last-named substances occurs almost as a rule in hepatic disease of any type, both experimental and clinical and, more significantly, there is a proportionately greater fall in serum albumin than in total protein, the globulin fraction may be either normal, increased, or decreased. Without entering into detailed discussion of the reasons for this development of hypoproteinemia, it may be said that the available evidence points to failure of the liver to furnish albumin or albumin-producing substances, with a disturbance in the dynamic equilibrium existing between stored and circulating protein.⁷ The obvious result is a fall in the colloid osmotic pressure of serum, a condition which favors transudation in regions of venous stasis. The full extent of this decrease in the osmotic properties of serum of patients with hepatic disease has only recently been appreciated. Butt and Keys⁸ have measured the colloid osmotic pressure by a modification of the method in which a membrane bag is used and have shown reductions to as little as half of the normal value, the observed pressures of practically all patients with ascites or edema are below the theoretical level at which transudation may occur. Furthermore, the figures of the named investigators show clearly that the observed osmotic pressure is not in linear relation to the total protein content of serum and that in about a third of the cases, sharp reductions in colloid osmotic pressure are noted even when the value for total protein is normal. Bollman's⁹ unpublished studies on the effects of plasmapheresis in animals with experimental cirrhosis have in general confirmed the above-mentioned observations, but they appear to show that there is no constant level of colloid osmotic pressure at which ascites invariably occurs. In other words, there are other variable factors presumably involving such matters as pressure in mesenteric capillaries and the degree of hepatic damage. The effects of meat extracts described in an earlier paragraph may involve such factors. Measurements of pressure in the portal system of subjects with cirrhosis are not as yet available, but such studies doubtless will be undertaken by physiologists, in the experimental animal. The problem of electrolyte and water distribution between circulating fluids and tissue fluids must also be investigated further since changes in osmotic pressure of the order of magnitude observed by Butt and Keys can scarcely be without some effect on the hydration and electrolyte content of individual cells.

Some of the major clinical problems yet to be solved by students of hepatic disease are concerned with the nature of hepatic insufficiency and with the cause of the hemorrhagic diathesis. On the first matter little information is available although the metabolic disturbances which occur in

⁷ HOLMAN, R. L., MAHONEY, E. B., and WHIPPLE, G. H. Blood plasma protein given by vein utilized in body metabolism. II. A dynamic equilibrium between plasma and tissue proteins, Jr. *Exper. Med.*, 1934, *ix*, 269-282.

⁸ BUTT, H. R., and KEYS, ANCEL. Colloid osmotic pressure, studies of normal individuals and of those with hypoproteinemia, *Proc. Staff Meet. Mayo Clinic*, 1937, *xii*, 566-570.

⁹ BOLLMAN, J. L. Unpublished data.

hepatectomized animals and in those with extreme hepatic injury have been extensively studied. One fact is certain, no form of hepatic damage, clinical or experimental, even approximates the picture of absolute hepatic insufficiency produced by total removal of the liver. The major metabolic properties are almost universally preserved even with maximal hepatocellular destruction. The most favored hypothesis of clinical hepatic insufficiency is that the detoxifying function of the organ is so altered that the increased susceptibility to endogenous and exogenous toxins produces a fatal issue before the entire function of the liver is lost.² The vulnerability of the damaged liver to infections, anesthetics, and hepatotoxins may be cited in support of this hypothesis, as well as the fact that the symptoms of the Eck fistula animal seem to be clearly attributable not so much to diversion of blood flow as to failure of detoxification. In addition to the hypothetical failure of this function, one must concede that other factors enter into the clinical picture of hepatic insufficiency. In the occasional case there are striking changes in the chloride content of blood and in the acid-base equilibrium, the factor of anoxic anoxemia which is quite constantly present in advanced hepatic disease also may not be without significant effect especially on those tissues which are particularly sensitive to oxygen want. There is good reason to believe that the condition of hepatic insufficiency is a reversible one, and the occasional recovery of a patient from profound hepatic coma gives hope that its physiologic nature may be known and controlled.

So far as the problem of hemorrhage in hepatic disease is concerned, it seems to be one manifestation of hepatic insufficiency, or at least the two often occur simultaneously. All factors necessary for normal coagulation of blood such as calcium, fibrinogen and thromboplastin are presumably present in normal amounts, leaving prothrombin as the only variable. Exact methods for the determination of these substances have not been developed but studies from a number of laboratories indicate that the hemorrhagic state in hepatic disease may depend on deficiency of prothrombin alone¹⁰ and that this in turn may be dependent on the exclusion of bile from the alimentary tract or on disruption of the mechanism by which prothrombin or some precursor is stored.

The possible relation of prothrombin to the hypothetical "Koagulations vitamin," the existence of which has been only recently recognized, was first brought under consideration by biochemical studies of the diseases of domestic animals. In such widely differing conditions as a specific deficiency disease of chicks, the toxic sweet-clover disease of cattle, prolonged obstructive jaundice and complete external biliary fistula, the prothrombin of the blood is reduced. Since the first two conditions respond to administration of vitamin K, it is reasonable to hope that the last two may be similarly affected. Chemically, prothrombin and vitamin K appear to have

¹⁰ QUICK, A. J., STANLEY-BROWN, MARGARET, and BANCROFT, F. W. Study of coagulation defect in hemophilia and in jaundice, *Am. Jr. Med. Sci.*, 1935, *CXC*, 501-511.

little in common, but there is indirect evidence pointing to some obscure interrelation between the two substances. Clinical data are almost completely lacking but the theoretical possibilities are exceedingly attractive.

Certain other fields of purely clinical research in hepatic and biliary disease which are being developed can only be mentioned here. Studies on the so-called biliary dyskinesia to which Westphal,¹¹ Ivy^{12, 13} and McGowan¹⁴ and his collaborators have contributed are furnishing an explanation of some hitherto obscure visceromotor phenomena as well as helping to explain the mechanism of the sphincter of the common duct and its relation to biliary pain.

The application of accurate physiologic methods to the clinical study of hepatic and biliary disease obviously is increasing our comprehension of the subject, but it is apparent that many crucial problems will have to be solved, not at the bedside alone but by the clinician and the experimental pathologist working in cooperation. The clinical application of facts already known and of others yet to be unearthed doubtless will be a slow process but it is equally certain that their utilization eventually will serve to expand present diagnostic and therapeutic horizons. Just as we owe our present facilities for the care of the diabetic patient to studies on the dog, so we may eventually attain some mastery of hepatic disease by continuation of experimental studies which at first seem far removed from the field of clinical medicine.

ALBERT M. SNELL

¹¹ WESTPHAL, KARL. Muskelfunktion, Nervensystem u. Pathologie der Gallenwege. I. Untersuchungen über den Schmerzanfall der Gallenwege und seine ausstrahlenden Reflexe, *Ztschr. f. klin. Med.*, 1923, **xcvi**, 22-51. II. Experimentelle Untersuchungen über die nervöse Beeinflussung der Bewegungsvorgänge der Gallenwege, *Ztschr. f. klin. Med.*, 1923, **xcvi**, 52-94. III. Die Motilitätsneurose der Gallenwege und ihrer Beziehungen zu deren Pathologie, zur Stauung, Entzündung, Steinbildung usw., *Ztschr. f. klin. Med.*, 1923, **xcvi**, 95-150.

¹² IVY, A. C., VOEGTLIN, W. L., and GREENGARD, HARRY. The physiology of the common bile duct, a singular observation, *Jr. Am. Med. Assoc.*, 1933, **c**, 1319-1320.

¹³ IVY, A. C., and SANDBLOM, PHILIP. Biliary dyskinesia, *Ann. Int. Med.*, 1934, **viii**, 115-122.

¹⁴ MCGOWAN, J. M., BUTSCH, W. L., and WALTERS, WALTERMAN. Pressure in the common bile duct of man, its relation to pain following cholecystectomy, *Jr. Am. Med. Assoc.*, 1936, **cv**, 2227-2230.

REVIEWS

Observations of a General Practitioner By WILLIAM N. MACARTNEY, M.D. 478 pages, 21 × 15 cm. The Gorham Press, Boston. 1932. Price, \$3.00.

Physicians actively engaged in the practice of medicine will like this salty volume with its first hand observations on disease and human beings interspersed with humorous anecdotes of varying degrees of savoriness. Those who are hospital physicians will be interested in the different types of disease seen in practice. There is much to think about in these chapters for the author includes his medical philosophy as well as his medical experience. He writes in vigorous and pungent short sentences and says his mind plainly. Therapy is particularly worth consideration because one feels he applied it himself and observed the results personally without an intervening screen of assistants, interns and nurses.

Altogether this is an entertaining and instructive book. Most of us will heartily disagree with a large number of the author's ideas but we will think all of them worth considering and tuck many a suggestion away in our mind for future trial.

M C P

Der Blutdruck Des Menschen By ESKIL KYLIN. 322 pages, 23.5 × 16 cm. Verlag von Theodor Steinkopff, Dresden and Leipzig. 1937. Price, RM 24.

The purpose of this book is to present the author's views as to the problem of abnormalities of blood pressure. It is therefore a discussion of the mechanisms involved in the maintenance of normal pressure and in the causation of hypertension and hypotension. It is not concerned except in a secondary way with the symptomatology of blood pressure derangements nor with therapeutic procedures. The first section deals with normal blood pressure, arterial, capillary and venous. This is followed by a very interesting discussion of modern concepts of blood pressure regulation, divided into chapters on central factors in blood pressure regulation, on peripheral mechanisms, and on the role of endocrine organs.

The subject of arterial hypertension is introduced by a section devoted to a general discussion of the varieties of disturbances or lesions which may lead to a higher level of blood pressure. The author is a strong advocate of the belief that the hypophysis secretes through an ependymal lined canal into the third ventricle. The character of the secretion alters the irritability of hypothalamic blood pressure regulating centers, and plays therefore a major role in essential hypertension. The evidence in favor of these views is marshalled in an ingenious way. The author devotes considerable space to an attempt to minimize the relationship between kidney lesions and hypertension. It is evident that he is not well acquainted with the foreign literature since he omits the fundamental experiments of Goldblatt and the most important references on the relation of polycystic disease to hypertension.

In the discussion of major clinical varieties of hypertension the author subdivides them into capillary and arterial forms of hypertension. He believes that diffuse glomerulo-nephritis is primarily a generalized capillary disease. No convincing proof of this assertion is offered.

Enough has been said perhaps to show that this volume will interest all students of the problem of hypertension. The author is learned, original and somewhat prejudiced in favor of his own opinions. Every internist can study the results with profit.

M C P

The Cardiac Glycosides By ARTHUR STOLL, D Sc, M D 80 pages, 25 × 17 cm
Pharmaceutical Press, London 1937

This treatise comprises three lectures delivered by Professor Stoll in the College of the Pharmaceutical Society of Great Britain under the auspices of the University of London. The first of these lectures is devoted to the importance of sugars in the plant economy and the classification of glycosides including a series of definitions of terms. In this lecture also the specific glycosides of digitalis and strophanthin are discussed. Great stress is laid on the structure of the sugars isolated from the cardiac glycosides. The historical features of the chemical and clinical events of significance in the development of these compounds are referred to in a very interesting manner.

The second lecture treats of the glycosides of squill and the hydrolysis and products of hydrolytic cleavage of scillaren A. The structures of the aglycones are discussed and compared. These structures are shown to be phenanthrene derivatives and related to the bile acids, sex hormones and toad venoms. The schemes of cleavages and the complex structures of the aglycones are especially well elucidated.

In the third lecture the author discusses the digitalis glycosides with special reference to botanical species variation. Methods of extraction are critically evaluated. The cardiac principles from *digitalis purpurea*, *ambigua* and *lanata* are compared. Comprehensive studies on the extraction of Digilamid from *digitalis lanata* are described. The author concludes that this crystalline glycoside is the only chemically pure digitalis glycoside of constant constitution. Its therapeutic dose for man orally is 0.75 mg daily. It is available also for intramuscular and intravenous medication.

The style of the author is lucid and the subject matter timely.

J C K, JR

Exophthalmic Goiter and Its Medical Treatment By ISRAEL BRAM, M D Second Edition 456 pages, 25 × 17.5 cm C V Mosby Company, St Louis 1936
Price, \$6.00

In his preface to this work, the author describes it as a "treatise on the etiology, diagnosis, and principles of the medical treatment of exophthalmic goiter, based on personal experience with over 5000 cases of this disease, observed within a period of over 25 years." In a footnote, he states that this number is included within the total of approximately 16,000 goiter cases observed.

After reading the book, one is forced to the conclusion that the author has been almost miraculously successful in curing a large series of cases of exophthalmic goiter, and in a strikingly short time. Statistically, he reports only 2600 cases, so that one wonders as to the results in the remaining 2400. Apparently 90 per cent of the 2600 cases were completely cured, as they were all well after being followed for periods of from 3 to 20 years, 10 per cent had minor residual symptoms. There were, therefore, no deaths in this group. Sixty-seven per cent of the cases were discharged from treatment after six months, 17 per cent are reported as continuing their customary duties while under treatment, and another 44.9 per cent abstained from their work for three months or less.

The author feels that surgical interference is usually contraindicated, and states that indications for thyroidectomy occur in a little over 2 per cent of all patients with Graves' disease. Surgery and radiation he classifies as local measures, to be used rarely. He places great emphasis on the danger and frequent occurrence of postoperative myxedema, and gives the impression that exophthalmic goiter with myxedema is very common in patients treated by methods other than his own.

One would feel more confidence in the author's statements if there were not so many obviously weak points in the book. The illustrations, 79 in number, are limited to photographs of patients, either before, or in many cases before and after treat-

ment The absence of photographs of histological sections of the thyroid gland is surprising Disappointing, too, is the section on basal metabolism, the term "basal metabolic rate" is not defined, is not described as a measurement of heat production of the body, nor is there any discussion of methods of determination of the rate

Literature is extensively quoted, but superficially reviewed, and opinions are given without reference to the date of the article Many antiquated observations are quoted, and it is usually impossible to tell their date from the text

In the final chapter, 55 cases are reported fairly fully except that the details of treatment are omitted

In the section on treatment, quinine is emphasized as a very important drug The therapeutic value of glandular extracts is reviewed, but, again, the author frequently quotes antiquated studies, for instance, in the discussion of the use of adrenal cortical extracts In this paragraph, he advocates the oral administration of pills of glycerinated cortical extracts Later, he advocates the oral use of ovarian residue in the presence of amenorrhea in the female

On the whole the book does not appear to be a safe guide The opinions expressed are contrary to the experience of most physicians and the data furnished will not induce those with an analytic faculty to alter their views

T N C

Pediatric Dietetics By N THOMAS SAXL, M D 565 pages, 24 × 15.5 cm Lea and Febiger, Philadelphia 1937 Price, \$7.00

Various works dealing with the diets of individuals in the pediatric age, have in the past been limited mostly to infant feeding The nutritional aspects of the child over two years of age has been relegated to the domain of adult nutritional problems Dr Saxl has presented the entire subject of pediatric dietetics in a separate volume The appearance of a work of this type is timely, for to quote Dr De Sanctis in his foreword to this volume "Lay periodicals, press and radio have persistently encouraged various types of diets for adults The vast majority of these are scientifically unsound and unfortunately have been applied to children"

The subject matter of this volume has been presented in three parts, subdivided into sections Into the first part the author condenses the mechanics and chemistry of digestion during infancy Explanation of the *modus operandi* and indications for use of the various basic constituent foods are also included in this section A comprehensive summary of accepted proprietary foods is also made In addition a brief statement of the nature, source and therapeutic use of vitamins is given

Part II deals with infant feeding, a section being devoted to breast feeding and one to the artificial method

Part III deals with dietetic management of pediatric diseases Physicians interested in various conditions have collaborated with Dr Saxl in the presentation of this section To those not sufficiently familiar with metabolic processes in pathological conditions this section will clarify a number of disease processes

The appendix is composed of numerous receipts, tables of weight, height, and foods Also, incorporated is a very exhaustive bibliography

The work in its entirety is written in a uniformly easy manner Much of the material is to be counted as superfluous, and much could be shortened without destroying completeness The volume represents a needed contribution, dealing with the nutritional needs of the child in disease and health It is a useful addition to the library of the practitioner

J E B

COLLEGE NEWS NOTES

GIFTS TO THE COLLEGE LIBRARY

The following gifts to the Library of Publications by Members are gratefully acknowledged

Books

- Dr Kenneth E Appel (Associate) and Dr Edward A Strecker (Fellow), Philadelphia, Pa, " Practical Examination of Personality and Behavior Disorders Adults and Children ",
Dr Jacob Gutman (Fellow), Brooklyn, N Y, Twelfth Supplement to " Modern Drug Encyclopedia ",
Dr George B Lake (Associate), Waukegan, Ill, " Parenteral Therapy "

Reprints

- Dr Robert A Black (Fellow), Chicago, Ill, three reprints,
Dr Nathan Blumberg (Fellow), Philadelphia, Pa, one reprint,
Dr Jacob M Cahan (Fellow), Philadelphia, Pa, one reprint,
Dr Mary Hoskins Easby (Fellow), Philadelphia Pa one reprint,
Dr G Philip Grabfield (Fellow), Boston, Mass, three reprints,
Dr P A Gray (Fellow), Santa Barbara, Calif, twelve reprints,
Dr Henry Joachim (Fellow), Brooklyn, N Y, seven reprints,
Dr Abel Levitt (Fellow), Buffalo, N Y, one reprint,
Dr Perry J Melnick (Associate), Decatur, Ill, one reprint,
Dr Paul H Ringer (Fellow), Asheville, N C, two reprints,
Dr James W Sherrill (Fellow) and Dr E F F Copp (Fellow), La Jolla, Calif, one reprint,
Dr Walter H Watterson (Fellow), LaGrange, Ill, one reprint,
Dr Edward E Woldman (Associate), Cleveland, Ohio, three reprints

Grateful acknowledgment is also made of the receipt of the following directories as gifts to the College Library

- Medical Society of the State of New York, through Dr Peter Irving (Fellow), New York City—" 1937 Medical Directory of New York, New Jersey and Connecticut ",
Bureau of Medicine and Surgery, U S N—September 1, 1937, issue of the " Navy Directory "

Dr Clement R Jones (Fellow), Pittsburgh, Pa, has donated to the College Library an original copy of the ANNALS OF MEDICINE, Volume I, No 1, April, 1920 This was the first issue of the first journal sponsored by the American College of Physicians and the American Congress on Internal Medicine, but during the intervening years and changes of administration, all official copies of this issue had disappeared It is an interesting addition to the College archives First, it is a very attractive and well-printed journal It contains the roster of the members of the American College of Physicians and of the American Congress on Internal Medicine up to March 1, 1920 In it appears the photographs of the Officers and Councilors of the College for that year, and photographs of the Convocation held on February 26, 1920, and of the Annual Banquet the same year, held at the Congress Hotel in Chicago The contents of the journal, including a comprehensive article

by the first President of the College, the late Reynold Webb Wilcox, M A, M D, LL D, D C L, F A C P, on "The Field of Internal Medicine," were made up of presentations by Louis A Turley, A M, M D, Ph D, F A C P, John A Lichty, M D, F A C P, F M Pottenger, A M, M D, LL D, F A C P, E H Reudiger, A B, M D, F A C P, Louis Faugetes Bishop, A M, M D, D Sc, F A C P, E L Tuohy, A B, M D, F A C P, F A McJunkin, A B, M D, F A C P, Hugo A Freund, A B, M D, F A C P, Bruce C Lockwood, A B, M D, and Frank Smithies, M D, Sc D, M A C P Dr Smithies was the Supervising Editor

MOTION PICTURE REELS

Mrs Louise K Smithies, widow of the late Dr Frank Smithies, former Secretary-General and former President of the College, due to Dr Smithies' long association with this College, has donated to the College Dr Smithies' two 35 mm reels showing his method of dilation of cardiospasm by the pneumatic expanding bougie These motion picture films are available, on loan, to members of the College who may wish to show them

THE TWENTY-SECOND ANNUAL SESSION OF THE COLLEGE

The Twenty-Second Annual Session of the College will be held in New York City, April 4 to 8, inclusive, 1938, with headquarters at the Waldorf-Astoria Hotel, 49th to 50th Streets, Park to Lexington Avenues Dr James H Means, of Boston, as President of the College, will have charge of the program of General Sessions and Special Lectures Dr James Alex Miller, of New York City, as General Chairman, will have charge of the program of Clinics and Round Tables

Last spring, the Executive Offices sent out a brief postal questionnaire to determine the desires of members with respect to program arrangements and items, particularly the Special Lectures, Round Tables and Clinico-Pathological Conferences

847 to 267 requested the retention of Special Lectures (these do not refer to the General Sessions, but to the series of special lectures given during the mornings, at the same time clinics are in session),

1046 to 101 favored the extension of the Round Table program,

1051 to 88 favored Clinico-Pathological Conferences on the program

Many members sent in very helpful suggestions about titles and speakers, and the Program Committee is carefully considering them

New York Hotel Rates—Hotel rates in New York City are, on the average, higher than in most other places At the Waldorf, which is one of the world's finest hotels, a special convention rate has been obtained, beginning at \$5 00 single (reduced from \$7 00), and beginning at \$7 00 double (reduced from \$9 00) In the immediate neighborhood—in fact, within one square of the Waldorf—there are several other good hotels with varying rates A list of such hotels may be obtained from the Executive Secretary of the College

The Executive Committee, composed of the chairmen of the various committees for the New York Session, is as follows Dr James Alex Miller, *General Chairman*, Dr James Ralph Scott, *Vice Chairman*, Mr E R Loveland, *Executive Secretary*, Dr Robert A Cooke, *Clinics*, Dr Russell L Cecil, *Round Tables*, Dr Howard F Shattuck, *Entertainment*, Dr Peter Irving, *Publicity*, Dr Edward P Eglee, *Local Transportation*, and Dr Willard J Denno, *Auditorium*

TESTIMONIAL TO DR POTTINGER

On September 26, 1937, former patients and friends of Dr F M Pottenger (Fellow), Monrovia, Calif, gathered in the gardens of the Pottenger Sanatorium for a dual celebration, the annual home-coming of former patients, and the celebration of Dr Pottenger's sixty-eighth birthday. More than 250 guests were present, many of whom came from points far-removed from the Pacific Coast, one from New York City.

Patients of the Pottenger Sanatorium who have been discharged as arrested or cured look upon themselves as 'alumni' and refer to their "class." The oldest alumnus present was one who had been a patient in 1903.

Appropriately inscribed, a beautiful sundial was presented to Dr Pottenger from the present patients. Other gifts were also presented and messages were received from all over the world.

Henry K Mulford, known to a host of members of the American College of Physicians as the founder of the H K Mulford Company, Philadelphia, and internationally known in the field of biological research, died during October at the age of seventy-one, after an illness of several days. Mr Mulford had more recently been the Director of the Research and Biological Laboratories of the National Drug Company, and President of the Mulford Colloid Laboratory. In connection with his early founding of the H K Mulford Company, he was directly in charge of making antitoxins and vaccines, the first in this country to interest himself in that line. He was graduated from the Philadelphia College of Pharmacy and Science in 1887.

Dr Clifford E Henry (Fellow), Minneapolis, Minn, has been advanced from the rank of commander to that of captain in the naval medical reserve corps. This rank is held by only four men in the country, and is next in line to that of rear admiral. Dr Henry is Minnesota's senior naval medical reserve officer.

The Mississippi Valley Medical Society of which Dr Harold Swanberg (Fellow), Quincy, Ill, is Secretary, offers a cash prize of \$100.00, a gold medal and a certificate of award for the best unpublished essay on a subject of interest and practical value to the general practitioner of medicine. Entrants must be ethical licensed physicians, residents of the United States and graduates of approved medical schools. The winner will be invited to present his contribution before the next annual meeting of the Mississippi Valley Medical Society (September 28 to 30, 1938), the Society reserving the exclusive right to first publish the essay in its official publication, *The Radiologic Review and Mississippi Valley Medical Journal*. Contributions shall not exceed five thousand words, shall be typewritten in English in manuscript form, submitted in five copies, and must be received not later than May 15, 1938.

Dr William B Grayson (Associate), Little Rock, Ark, was recently re-appointed state health officer for a second term of four years.

Dr William E Gardner (Fellow), Louisville, Ky, was made President-Elect of the Kentucky State Medical Association for 1937-38 at its annual meeting during September.

Dr Frank M Stites, Jr (Fellow), Louisville, was elected a Vice President. The 1938 meeting of the Association will be held in Louisville.

Dr Hubert C King (Fellow), Lakewood, Ohio, and Dr Karl D Figley (Fellow), Toledo, Ohio, are members of the subcommittee of the newly-organized Speakers' Bureau of the Ohio State Medical Association, formed for the purpose of assisting county and district medical societies in obtaining outside talent for their programs. It is anticipated that the facilities of the Bureau will later be made available for meetings of allied and lay groups.

Major General Charles R Reynolds (Fellow), Surgeon General of the U S Army, addressed the annual "Mercy Day" celebration of the Mercy Hospital in Pittsburgh on September 23, his subject being "Medicine in the Military Service"

Dr William D Stroud (Fellow and Treasurer), Philadelphia, Pa, addressed the Forty-third annual meeting of the Utah Medical Association of Salt Lake City, September 2 to 4, on "Etiology of Cardiovascular Disease, Coronary Diseases Including Angina Pectoris, Clinical Efficacy of Digitalis Preparations"

Under the presidency of Dr J Morrison Hutcheson (Fellow and Governor), Richmond, Va, the Medical Society of Virginia held its Sixty-Eighth Annual Session at Roanoke, October 12 to 14

A sectional meeting and dinner of the Fellows and Associates of the American College of Physicians was held at the Shenandoah Club in Roanoke on October 12 during the course of the State meeting. Dr J W Preston (Fellow), Roanoke, was Chairman of the local committee on arrangements for the sectional College meeting.

Dr Paul A O'Leary (Fellow), Rochester, Minn, is Secretary General of the Tenth International Congress of Dermatology and Syphilology to be held in New York City during September, 1940

Dr Warfield T Longcope (Fellow), Baltimore, Md, delivered the Gordon Wilson Lecture on "The Varieties of Hemorrhagic Nephritis and Their Prognostic Significance" before the Fifty-Fourth Annual Meeting of the American Clinical and Climatological Association in Baltimore, October 11 to 13

Under the presidency of Dr William H Cade, Jr (Associate), San Antonio, Tex, the Southern Psychiatric Association held its annual meeting at San Antonio, October 8 to 9. Among the invited guests on the program were the following: Dr George T Harding (Fellow), Columbus, Ohio—"Periodicity of the Manic-Depressive Psychoses", Dr C Charles Burlingame (Fellow), Hartford, Conn—"Can the Point of View and Technic of Private Practice Be Carried into the Mental Hospital", and Dr George R Hermann (Fellow), Galveston, Tex—"Neurocardiac and Neurocirculatory Disorders"

Dr Herman M Baker (Fellow), Evansville, Ind, will start the new year as President of the Indiana State Medical Association on January 1, 1938

Dr Hugo A Freund (Fellow), Detroit, Mich, has been appointed a member of the city Public Welfare Commission

Under the presidency of Dr George A Young (Associate), Omaha, Nebr, the Omaha Mid-West Clinical Society held its fifth annual assembly, October 17 to 22

Among the invited guest speakers were Dr William J Kerr (Fellow and President-Elect), San Francisco, Calif—"The Anxiety States in General Practice", Dr Hans H F Reese (Fellow), Madison, Wis—"The Constitution and the Biochemical Evaluation of the Nervous Patient", and Dr Thomas Parran (Fellow), Surgeon General of the U S Public Health Service—"Syphilis and the Public Health"

Dr William B Porter (Fellow) Richmond Va, was recently awarded the Jefferson Gold Medal of the Virginia Academy of Science

Dr Vincent J Dardinski (Associate), Washington, D C, has been appointed full time Pathologist and Director of the Laboratories of the Georgetown University Hospital Dr John R Cavanagh (Associate), Washington, D C, Associate Clinical Professor of Medicine at the University, will become Director of the Outpatient Department of the Hospital Dr Frank S Horvath (Associate), Associate Professor of Clinical Medicine, will be Assistant Director and Supervisor of Student Instruction in the Outpatient Department of the Hospital

Dr Russell M Wilder (Fellow), Rochester, Minn, addressed the clinical session of the New York Diabetes Association on October 15 on "Pathogenesis and Etiology of Diabetes"

Dr Nelson W Barker (Fellow), Rochester Minn, has been elected Secretary of the Southern Minnesota Medical Association

Under the presidency of Dr Charles E Sears (Fellow), Portland, Ore, the Oregon State Medical Society held its Sixty-Third Annual Session at Salem, October 21 to 23 Dr Lester R Dragstedt (Fellow), Chicago, Ill, was one of the guest speakers, his subjects being "Pathogenesis and Surgical Treatment of Duodenal Ulcer" and "Pathogenesis and Surgical Treatment of Acute Intestinal Obstruction"

Dr Louis F Bishop, Jr (Fellow), gave a talk on "Exercise in the Treatment of Chronic Cardiovascular Disease" before the Section on Medicine of the 16th Annual Scientific and Clinical Session of the American Congress of Physical Therapy on September 22, 1937, in Cincinnati

On Sunday October 2, 1937, Dr Bishop, Jr, also gave a talk (on invitation) on "Is It Safe for the Heart Patient to Fly?" before the Ninth Annual and First International Meeting of the Aero Medical Association of the United States, Hotel Waldorf Astoria, New York, October 3, 1937

REGIONAL MEETING OF MICHIGAN MEMBERS

A regional meeting of the Michigan Fellows and Associates of the College was held in Detroit, November 17, under the Governorship of Dr Henry R Carstens Dr Hugh Freund of Detroit assisted in the arrangement of the program, and the Harper Hospital acted as host Clinical presentations were given at the Harper Hospital from 4 00 to 6 30 p m, followed by a social hour and dinner Dr James D Bruce, Regent of the College, Ann Arbor, addressed the group on matters of interest about the College, and Dr A B Brower, College Governor for Ohio, Dayton, gave an address on "Hypotension" A large and representative group was present

OBITUARIES

LT COL LEROY T HOWARD

Lieutenant Colonel Leroy T Howard (Fellow), Medical Corps, U S Army, died suddenly in Washington, D C , on September 30, 1937

Colonel Howard, a native of the District of Columbia, was born October 27, 1888 He was a graduate of the Georgetown University, from which he received his medical degree in 1913 Following this he interned for one year in St Francis' Hospital, Jersey City, N J He was commissioned a First Lieutenant in the Medical Reserve Corps on September 29, 1916, and shortly thereafter he was called to active duty and pursued a course of instruction at the Army Medical School, Washington, D C , from October 14, 1916, to March 28, 1917 He was commissioned in the Regular Army as First Lieutenant, Medical Corps, on April 16, 1917, promoted to Captain March 28, 1917, Major May 27, 1918, and Lieutenant Colonel March 3, 1937 He was returned from duty in Hawaii March 29, 1937, on account of illness and was on sick leave pending retirement for disability at the time of his death

Colonel Howard was a specialist in neuro-psychiatry and served in that capacity at several of the largest hospitals in the Army During the World War he served in France He had been a Fellow of the American College of Physicians since 1932

W L SHEEP, M D , F A C P ,
Colonel, Medical Corps, U S A

DR RICHARD BARRETT OLESON

Dr Richard Barrett Oleson (Fellow), of Lombard, Illinois, died on August 6, 1937, at the Johns Hopkins Hospital Death ensued as a result of a septicemia following a prostatic operation

Dr Oleson was born in Bloomington, Ill , in 1870 His preliminary education was obtained in the public schools of Bloomington, Columbus (Ohio), and Lombard He completed his preparation for college at Wheaton College Academy, Wheaton, Ill Later, he attended the University of Wisconsin He received his degree of Doctor of Medicine from the Northwestern Medical School in 1893, and immediately thereafter served an internship of eighteen months' duration at the Cook County Hospital For some years he was Medical Attendant at the Country Home for Convalescent Children, at Prince Crossing He served one year as Clinical Assistant in the Dispensary of the Johns Hopkins Hospital, 1919-20

For many years he practiced Internal Medicine, specializing in Gastroenterology, in Lombard He was widely known throughout his neighborhood, and highly respected as a physician of exceptional ability and character At one time he did postgraduate work at the Trudeau School of Tubercu-

lois, Saranac Lake, N Y He contributed a number of excellent articles to the literature, and was active in medical society work He was a member of the Chicago Medical Society, the Illinois State Medical Society, the American Medical Association and was a Fellow of the American College of Physicians since 1922

Dr Oleson will be sorely missed in the community which has suffered this loss For years he had given superior medical service to the people among whom he lived, and he enjoyed a wide reputation The profession has lost an outstanding man who rendered excellent service to the people whose good fortune it was to have known him

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Governor for Northern Illinois

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“ The Acute and Subacute Pulmonary Involvement in Rheumatic Fever with Notes on the Complication of Basal Pulmonary Collapse ” by Dr Benjamin A. Gouley, pages 626-636, October ANNALS OF INTERNAL MEDICINE. The last four references in the text were not included in the reference list at the end of the article. They are as follows:

- 11 WENCKEBACH, K. Verhandl. d. deutsch. Gesellsch. f. Kreislaufforsch., 1935, viii, 32
- 12 SCHOEN, R. Die Pneumonose, Verhandl. d. deutsch. Gesellsch. f. Kreislaufforsch., 1935, viii, 94
- 13 PARKER, F., JR., and WEISS, S. Significance of lung changes in mitral stenosis, Am. J. Path., 1936, \ii, 573
- 14 EWART, W. Practical aids in the diagnosis of pericardial effusion in connection with the question of surgical treatment, British Med. J., 1896, i, 717



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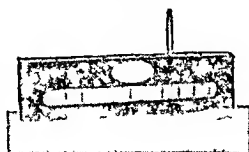
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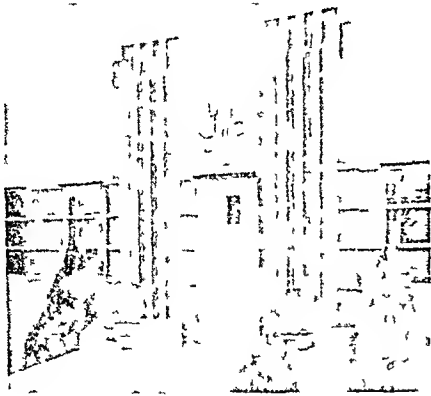
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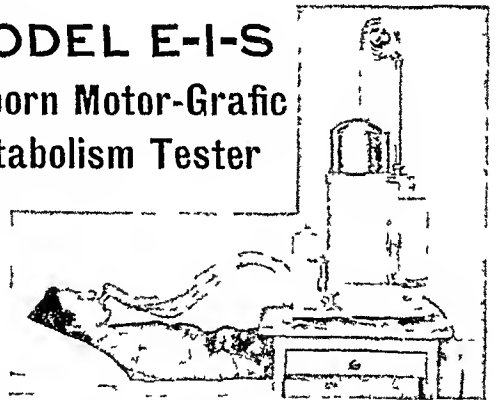
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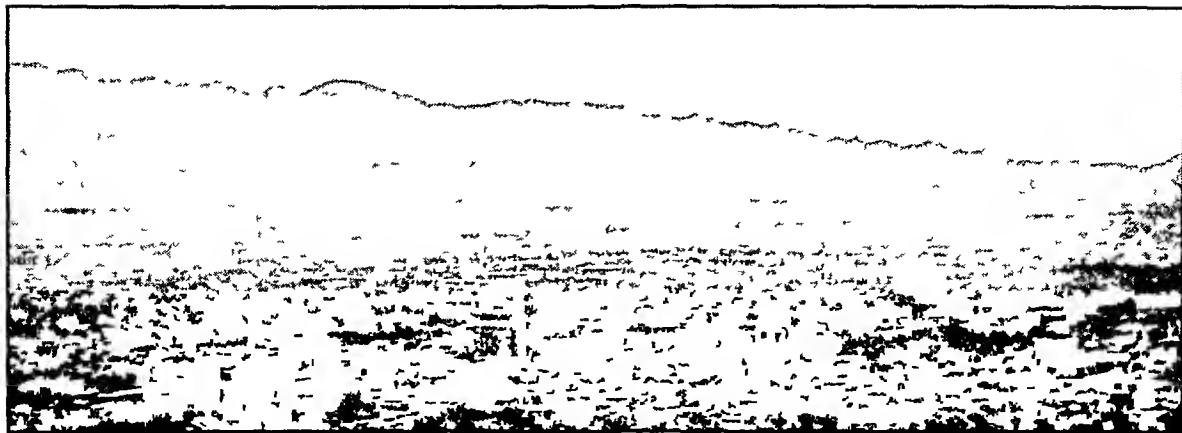
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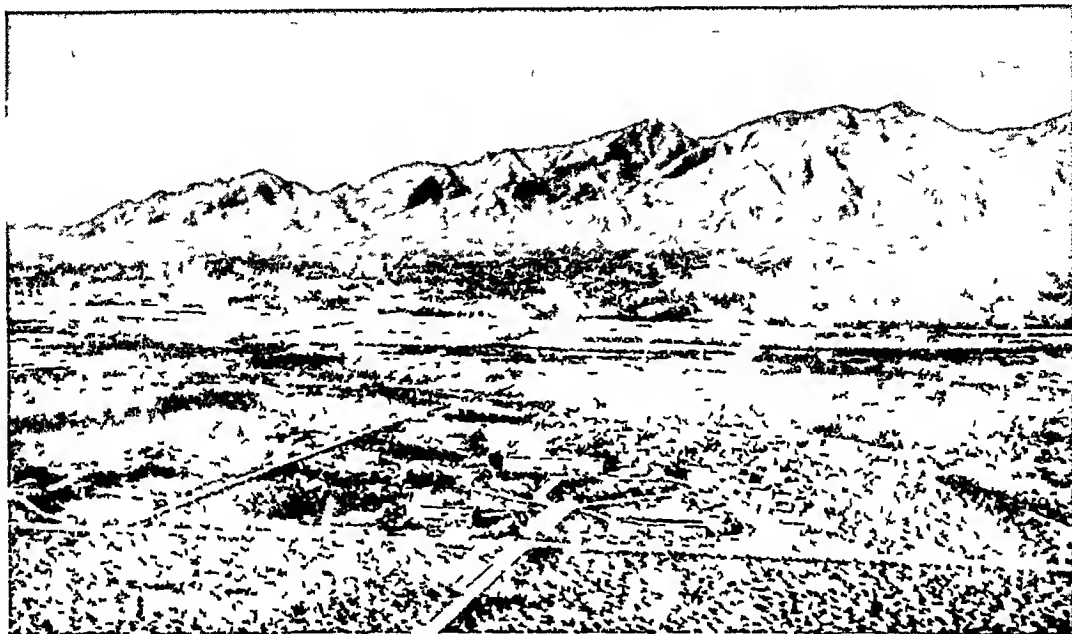


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Executive Office—4200 Pine Street,
Philadelphia, Pa

THE ANNALS OF INTERNAL MEDICINE is published by the American College of Physicians. The contents consist of contributions in the field of internal medicine, editorials, book reviews, and a section devoted to the affairs of the College.

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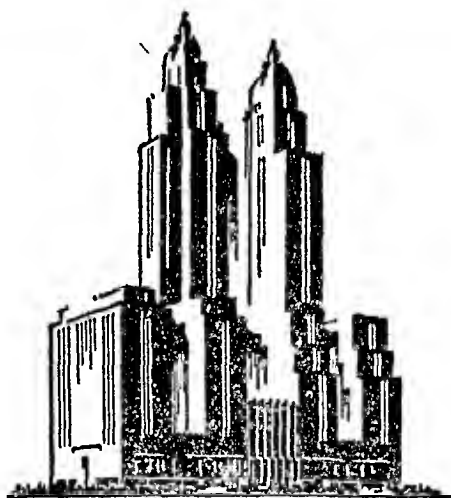
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DECEMBER, 1937

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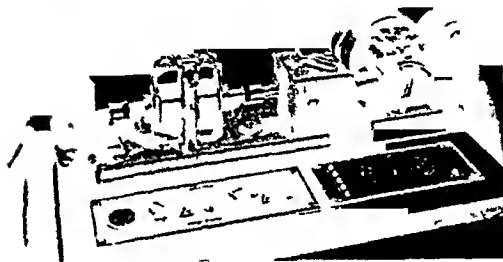
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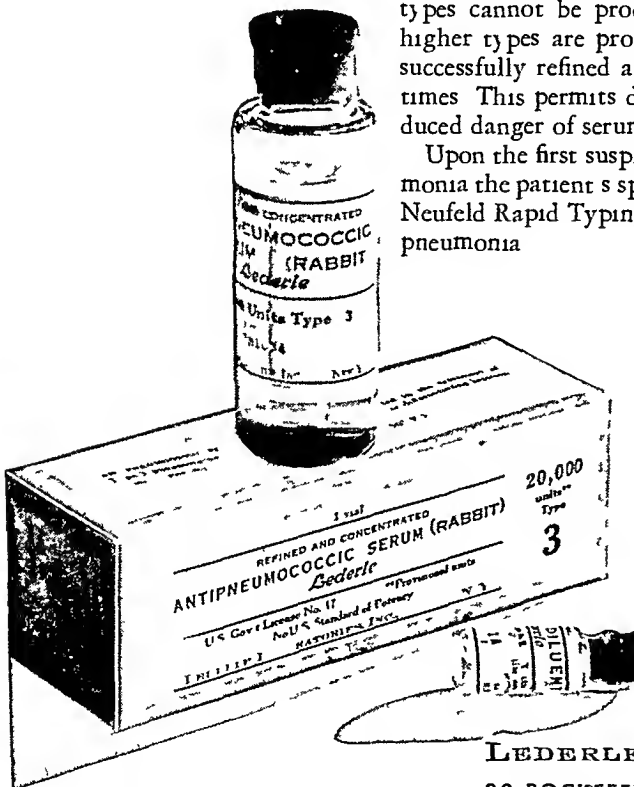
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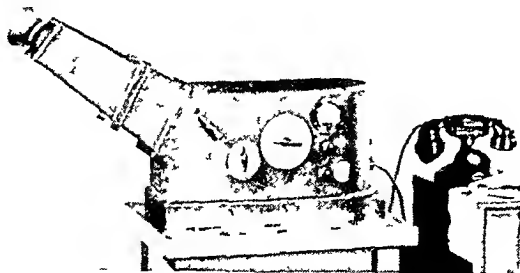
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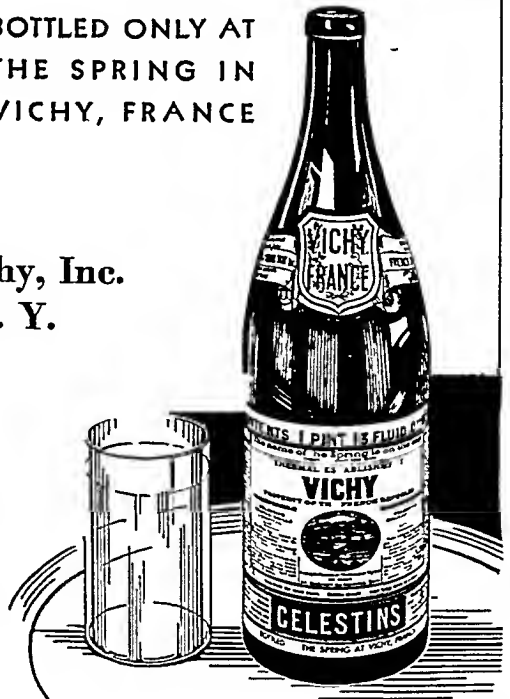
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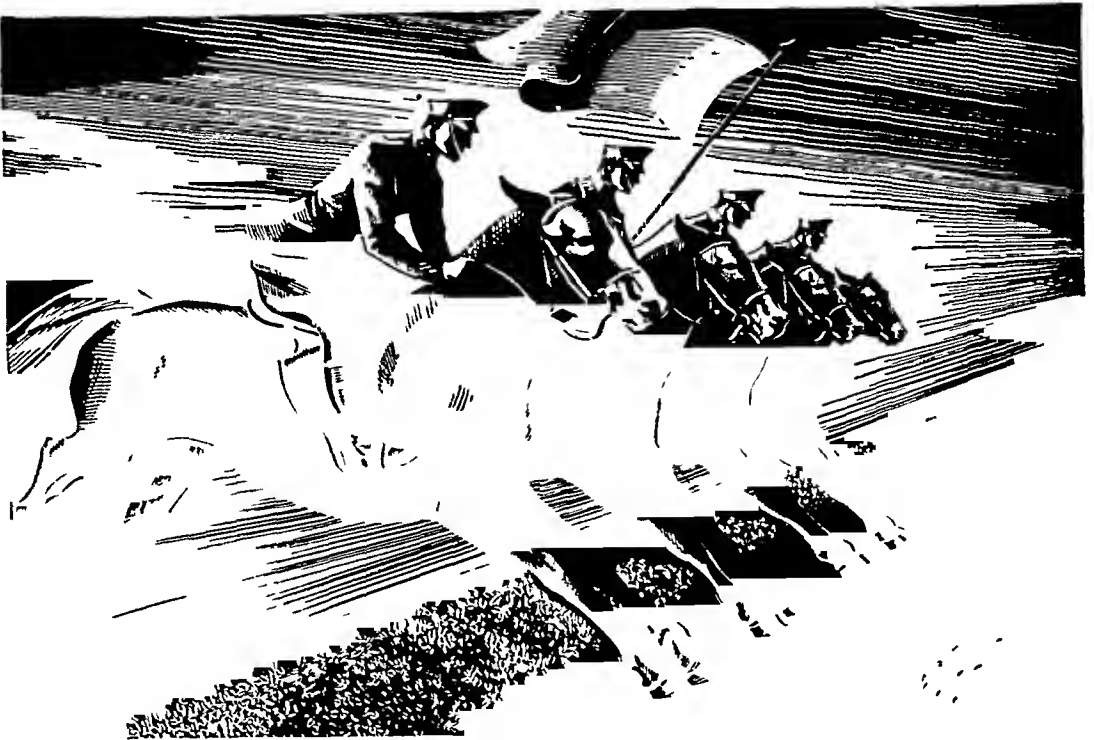


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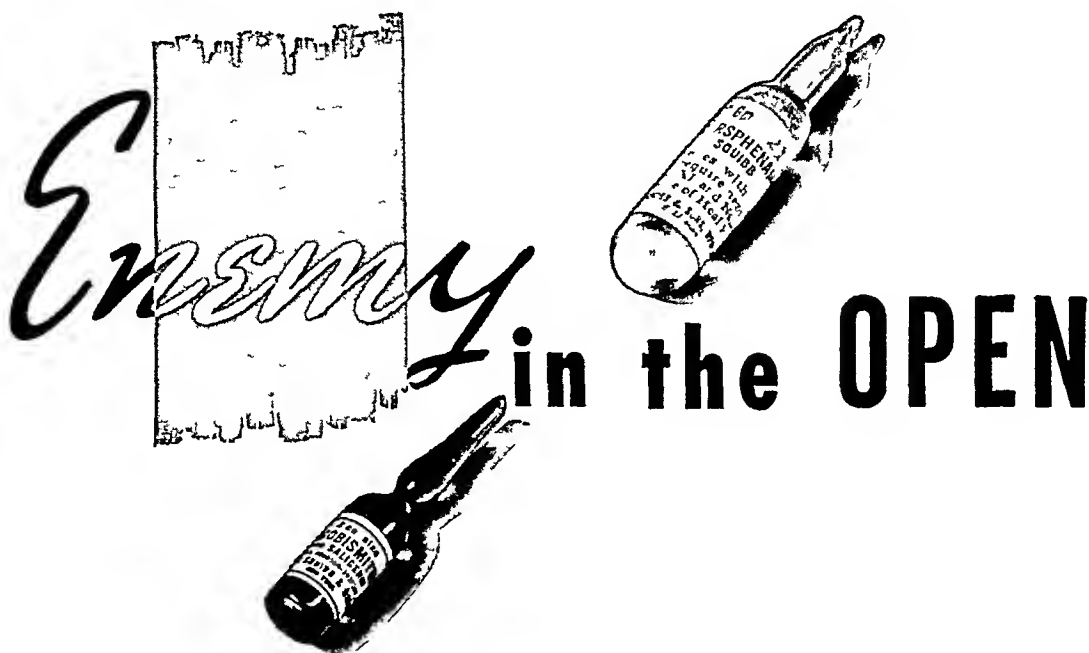
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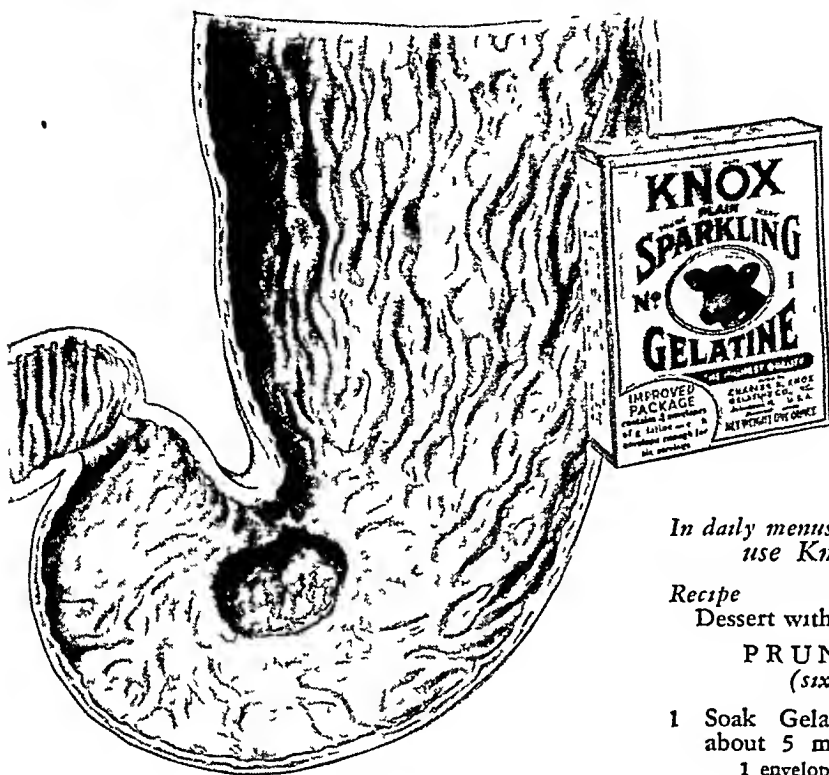
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 - 2 egg whites, stiffly beaten
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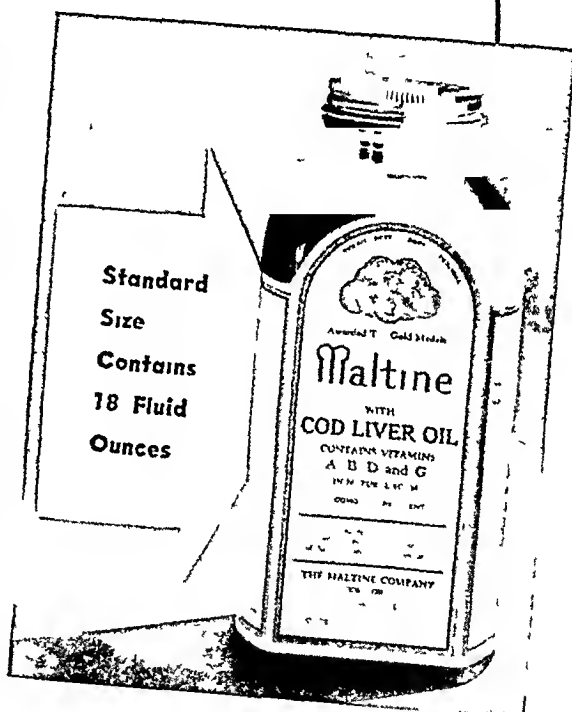
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ANNALS OF INTERNAL MEDICINE

VOLUME 11

DECEMBER, 1937

NUMBER 6

PLASMA COLLOID OSMOTIC PRESSURE AS A FACTOR IN EDEMA FORMATION AND EDEMA ABSORPTION *

By ARTHUR C. KERKHOFF, B S., Ph D., M D., *Minneapolis, Minnesota*

THE proteins of the blood plasma being hydrophilic colloids in solution must exert an osmotic pressure. This osmotic pressure measures the momentum of the impacts made by the colloid particles on a unit of surface. Water and salt will pass from the outside to the inside of a tube whose wall is permeable to salt and water but is not permeable to colloid particles if there is a salt solution within the tube containing a hydrophilic colloid dispersed in it. Water and salt entering the tube increase the hydrostatic pressure of the fluid within it until this hydrostatic pressure exactly equals the colloid osmotic pressure. Water and salt will be filtered out of such a tube if the hydrostatic pressure within the tube is higher than the colloid osmotic pressure. This process is known as ultrafiltration and the filtration of water and salt proceeds until the concentration of the colloid within the tube is such as to determine a colloid osmotic pressure equal to the hydrostatic pressure.

The walls of the capillaries are ultrafilters. They allow salts and water to filter through them in both directions but in their normal state they tend to prevent the filtration of the plasma proteins across their walls. The permeability of an ultrafilter membrane can be changed so that it will allow not only water and salts through it but also colloid particles of various sizes. Under these circumstances it is a "leaky" ultrafilter membrane and the fluid on both sides of the membrane will contain colloid. The first problem is to determine whether edema fluid is a pure ultrafiltrate containing salts and water in the same proportions as in the blood plasma but with very little or none of the proteins of the plasma. In order to determine this we have examined specimens of edema fluid (anasarca) from eight cases of nephritis and have found the total plasma proteins in this fluid to vary from 0.04

* Received for publication March 29, 1937.

From the Department of Medicine of the University of Minnesota at the Minneapolis General Hospital.

per cent to 0.25 per cent (table 1) The mean value is 0.13 per cent We have also examined the ascites of a dog made edematous within a period of

TABLE I
Examination of Edema Fluid in Nephritis and Nephrosis

Patient	% Protein in Edema Fluid	Edema Fluid		Plasma		Diagnosis
		Mg % Na	Mg % Cl	Mg % Na	Mg % Cl	
G L	07%	333	452			Acute glomerulonephritis
H N	04%					Subchronic glomerulonephritis with nephrotic element
E V	16%					Subchronic glomerulonephritis with nephrotic element
E V	25%					Subchronic glomerulonephritis with nephrotic element
S	19%	340	408	335	393	Nephrosis
S	16%	326	398	338	387	Nephrosis
G F C	07%					Subacute glomerulonephritis
G F C	08%					Subacute glomerulonephritis

24 hours by reducing the plasma proteins in his blood and we have found the percentage of protein in this fluid to be 0.14 per cent In five cases of chronic heart failure the amount of protein in edema fluid has varied from 0.1 per cent to 0.51 per cent, the mean value being 0.28 per cent (table 2)

TABLE II
Examination of Edema Fluid in Cardiac Failure

Patient	% Protein in Edema Fluid	Edema Fluid		Plasma		Diagnosis
		Mg % Na	Mg % Cl	Mg % Na	Mg % Cl	
C	27%	308	373	319	351	Congestive heart failure due to hypertension coronary disease
G	23%	338	384	353	398	Congestive heart failure due to mitral disease
B	51%	335	406	346	380	Congestive heart failure due to hypertension coronary disease
E	29%	335	393	337	366	Congestive heart failure due to mitral disease
H W	1%					Congestive heart failure Mitral stenosis

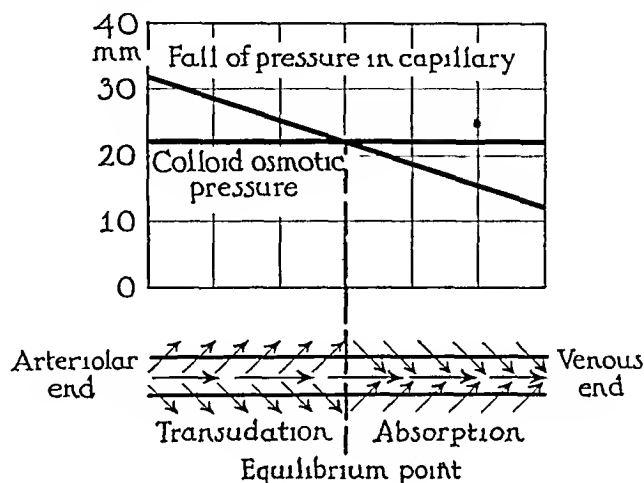
These somewhat higher values in heart failure are probably explained by the fact that the increased capillary pressure which increases the tendency to filtration in heart failure is accompanied by a dilatation of the capillaries and stasis Landis¹ has shown that stasis and dilatation can bring about some leakage of protein through a normal capillary ultrafilter There is

also frequently a tendency to anoxemia in heart failure Essex and Ort² have shown that anoxemia alters the permeability of the capillaries Our values for edema fluid are in essential agreement with the protein concentrations in anasarca fluid found by Darrow, Hopper and Cary,³ Leiter,⁴ Shelburne and Egloff,⁵ and Landis¹ Beckmann⁶ on the other hand has found higher concentration of protein in anasarca fluid but even the highest figures are less than many of the values found for lymph from a dog's leg by Drinker and Field^{7, 8} and by Weech, Goettsch and Reeves⁹ We were very careful to avoid contamination with blood in collecting our specimens The edema fluid was allowed to flow freely from the Southey tubes inserted into the subcutaneous tissues for at least a half hour before collecting in test tubes for chemical examination It is reasonable to assume from our figures that the capillary is a fairly good ultrafilter during the process of formation of edema in nephritis but is probably a little more "leaky" in heart failure

THE MECHANISM OF EDEMA FORMATION

Starling¹⁰ paved the way to an understanding of the mechanism of edema formation when he performed his perfusion experiments on dogs His experiments proved definitely that the presence of colloid within the perfusion fluid decreased the tendency to edema Edema occurred when only salts and water were used as perfusion liquid Before the abnormal conditions may be discussed, it is necessary that one analyze the normal mechanism of fluid exchange in the tissues We know from the work of Landis¹¹ that there is a gradual pressure fall along the capillary Normally the average pressure at the arterial end of the capillary is 32 mm Hg At the venous end of the capillary, the pressure is about 12 mm Hg and at the middle of the capillary loop about 22 mm Hg This, of course, is exactly what was predicted by Starling and Schade¹² in their early discussions of the subject, but until the work of Landis actual values for these pressures were unknown This capillary pressure tends to force water and salt through the capillary wall and out into the tissue spaces The colloidal osmotic pressure opposes this tendency for water and salt to leave the capillaries From values we shall present later, it will be seen that the average colloidal osmotic pressure in man is 22 mm Hg and therefore exactly equals the hydrostatic pressure within the capillary at the middle of the loop It is therefore quite obvious that at the arterial end of the capillary, water and salt will be forced out of the vessel into the tissue spaces as long as the hydrostatic pressure is greater than the osmotic pressure When these two pressures become equal, as they do in the middle of the capillary, fluid and salt will enter into the vessel as fast as they leave and no loss or gain will occur At the venous end of the capillary, however, the osmotic pressure is higher than the hydrostatic pressure and therefore water and salts will stream into this half of the tube Therefore in a normal capillary the amount of fluid

and salt forced out of the capillary at its arterial end will be approximately equalled by the amount of water and salt "pulled" into this tube at the venous end. We have modified Schade's original diagrams of fluid exchange in the capillary. Figure 1 represents the normal mechanism of fluid exchange along the capillary.



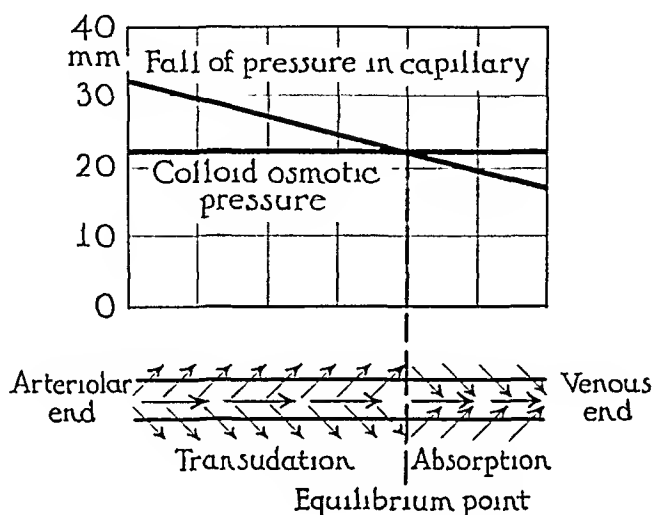
Normal mechanism

FIG 1 Graphic presentation of fluid exchange in the capillaries

Hydrostatic pressure and colloid osmotic pressure are not the only factors involved in edema formation. From this very simple discussion of normal fluid exchange in the capillaries, it appears obvious that the following factors might cause increased transudation and lead to edema formation: (1) increased hydrostatic or capillary pressure, (2) decreased plasma colloid osmotic pressure, (3) increased permeability of the capillaries, and (4) increased colloid osmotic pressure in the tissue surrounding the capillaries. Of these factors we believe that the increased hydrostatic pressure and the decreased osmotic pressure within the capillary are the most important. The hydrostatic pressure of edema fluid within the tissues themselves can not be wholly disregarded. In one case of edema due to heart failure we found this hydrostatic pressure to be approximately 8 cm of water. This would decrease the active filtration pressure by just that much and thereby decrease the tendency to formation of further edema.

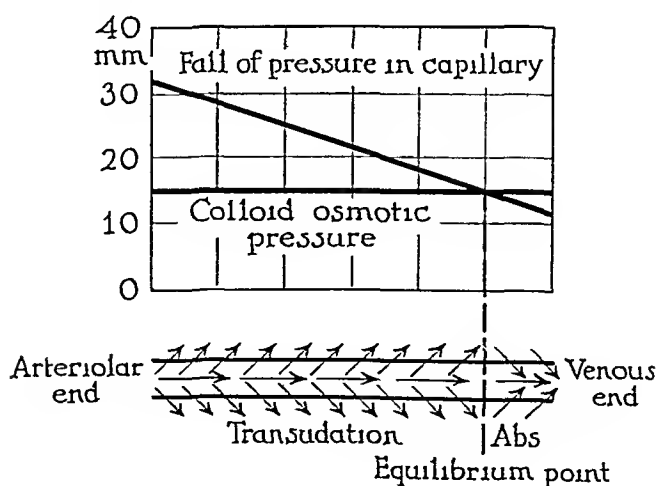
Let us now see what will happen if we vary some of the forces normally active in fluid exchange. If, for instance, we should increase the venous pressure, the point of balance between hydrostatic pressure within the capillary and osmotic pressure of the plasma colloids will shift towards the venous end of the capillaries (Figure 2). This will allow more fluid to pass out of the capillary since a greater proportion of the capillary will have a hydro-

static pressure higher than the osmotic pressure. If this process continues for any length of time it is obvious that edema must result. This is what happens when the right heart fails and the venous and capillary pressures rise in consequence of this heart failure. If instead of increasing the venous pressure we should decrease the colloid osmotic pressure (figure 3) and the



Mechanism with increased venous pressure (congestive heart failure)

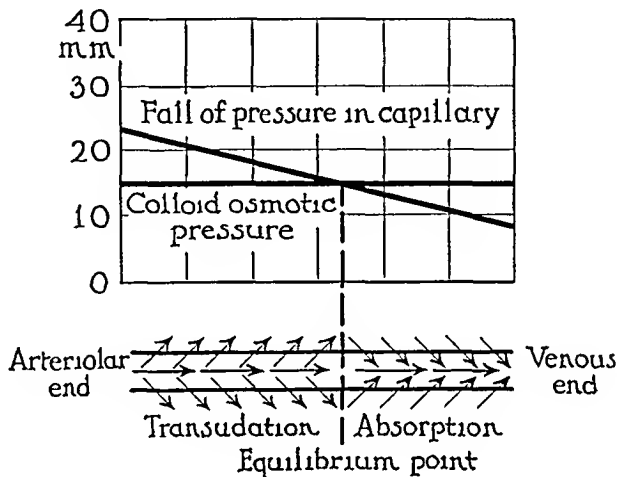
FIG 2 Graphic presentation of fluid exchange in the capillaries



Mechanism with reduced colloid osmotic pressure

FIG 3 Graphic presentation of fluid exchange in the capillaries

capillary pressure remains the same, the equilibrium point will again shift to the venous end of the capillary and more of the capillary will be given over to transudation and less to absorption. This also would lead to edema formation. In our opinion this is exactly what happens in nephrosis and nephritis with edema. At this point it might be well to consider that the body might accommodate itself to this lowered colloid osmotic pressure by reducing capillary pressure. If such should occur, a state might be reached much as is diagrammatically represented in figure 4. It is possible that this



Possible compensatory vascular mechanism with reduced colloid osmotic pressure

FIG 4 Graphic presentation of fluid exchange in the capillaries

mechanism is at times called upon for we shall see that certain reductions in colloid osmotic pressures can occur without edema. Below a certain value edema will practically always result because the body can not accommodate itself to these very low colloid osmotic pressures.

Up to the present we have not taken into consideration the possibility that there could be an increased permeability of the capillaries. In our discussion of the capillary wall as an ultrafilter we have stated that very little protein leaks through, so that if the capillary has become more permeable, it apparently has become more permeable only to salts and water. Such a permeability would not alter the mechanism of edema formation unless a change in permeability would occur only in one end of the capillary and not the other. If we assume, and it appears logical to do so, that the changes in permeability must of necessity occur throughout the whole capillary, then any such change would make no difference in the amount of edema. It

* In acute and chronic nephritis heart failure is often present also and the increased capillary pressure is an added factor in edema formation.

is obvious that if more fluid is forced out of the capillary in the arteriolar end, more fluid will also be re-absorbed into the capillary at the venous end, so that although more fluid may pass through the capillary wall in both ways, the end result is the same

If the capillary wall loses its property of holding back colloid particles then there will be a colloid osmotic pressure developed by the protein particles in the filtrate on the outside of this "leaky" capillary. This colloid osmotic pressure of the proteins in the filtrate surrounding the "leaky" capillary will tend to increase the filtration rate across the wall at the arterial end of the capillary and to decrease the absorption of fluid at the venous end. In other words the "leaky" ultrafilter tends to reduce the effectiveness of the osmotic pressure of the proteins within the capillary by exactly the amount of colloid osmotic pressure present in the ultrafiltrate on the outside. Calculations of the actual colloid osmotic pressure of concentrations of serum proteins of the order of those found in edema fluids show them to be negligible as factors in edema formation

THE MEASUREMENT OF COLLOID OSMOTIC PRESSURE

Starling¹⁰ was the first to measure the osmotic pressure of the plasma colloids. He obtained a value of 30 to 41 mm Hg for the normal osmotic pressure of the plasma colloids. From values of the capillary pressure given by Landis,¹¹ we know that these original measurements were far too high. This can be accounted for by his method which was to take concentrated serum, determine the colloid osmotic pressure and calculate the normal osmotic pressure on the basis of a straight line relationship between concentration and pressure, thereby disregarding the very large relative volume of the colloid particles or the "b" factor of the Van der Waals equation for the relation between pressure and volume of a gas. Other errors also crept into his method, such as inconstancy of temperature and the long time necessary for completion of the experiment which allowed changes to occur in the protein micel. Later Verney¹³ in Starling's laboratory used a modification of the Starling method and obtained values from 22.8 to 25 mm Hg. Krogh¹⁴ in 1929 obtained a value of 27.9 mm Hg. Govaerts¹⁵ in 1924 found pressures of 25.7 to 29.4 mm Hg in the normal and in cases of nephritis with edema 8.8 to 9.6 mm Hg. Landis¹⁶ in 1930 using a method similar to Starling's obtained a value of 18.3 mm Hg for normal osmotic pressure. Kylin¹⁷ in 1929 obtained a value of 30 mm Hg and Muntwyler, Way, Binns and Myers¹⁸ in 1933 found the normal osmotic pressure to be from 21.7 to 25.2 mm Hg. After Sørensen¹⁹ had laid the foundation for the dynamic determination of the colloid osmotic pressure, Schade¹² saw the advantages in this method and perfected a microtechnic. We have used the Schade method in all our determinations. This does away with all the disadvantages of the Starling method in that the temperature is kept constant so that the osmometer will not act as a thermometer. The plasma is used

in its normal concentration and the entire experiment requires only 2 to 4 hours. We have been able to demonstrate with our method that the above mentioned factors can cause great differences in the pressure readings. For example, using our method a sudden change in temperature of 0.1 of a degree C can give errors of the order of 25 per cent. We have also determined that allowing sterile plasma to stand at room temperature for 48 hours may increase the osmotic pressure as much as 19 per cent. Since in this method we are actually performing ultrafiltration and not measuring the osmotic pressure of the plasma against water or any other solution, there will be no difference in ionic concentration on the two sides of the membrane other than that brought about in accordance with the Donnan equilibrium. We are therefore actually measuring the colloid osmotic pressure as it affects ultrafiltration in the human capillaries or in other words the "effective" colloid osmotic pressure.

NORMAL COLLOID OSMOTIC PRESSURE OF THE BLOOD PLASMA IN MAN

We²⁰ have examined colloid osmotic pressure in 22 normal persons and have found the mean pressure to be 21.4 mm Hg at 37° C (table 3). The experimental error of our procedure showed a standard deviation of the

TABLE III
Normal Colloid Osmotic Pressure Values in Man

Case	Albumin	Globulin	Fibrinogen	Total Prot	Osmotic Pressure mm Hg at 37° C
W S					19.8
W C					19.7
E C					20.6
E G					20.2
R H					25.1
V A					18.4
W H					22.6
E B					22.6
B					19.9
O F					23.1
G K					20.9
A. F					17.9
K S					20.0
G J					19.4
L					25.2
B					25.6
P J					17.0
A M	3.85%	1.86%	70%	6.41%	23.7
H	4.49%	2.00%	41%	6.9%	22.3
H	4.49%	1.96%	36%	6.81%	20.8
S	4.39%	2.18%	67%	7.24%	23.1
S	4.03%	2.00%	64%	6.67%	20.5

Mean Pressure 21.4

Standard deviation 2.5

These values are not corrected for the error due to the addition of sodium oxalate as the anti-coagulant.

mean of 0.6 mm Hg or a probable error of the mean of 0.4 mm Hg. The biological scatter is measured by a standard deviation of ± 2.5 mm Hg. The values ranged from the lowest value of 17 mm Hg to the highest value of 25.3 mm Hg. Our mean agrees very well with the mean value for pressure in the middle of the human capillary as determined by Landis' measurements. Values very much higher than these would lead to an absorption of the body fluids into the blood vascular system, their excretion through the kidneys, and a consequent dehydration of the body. Values much lower than these would lead to generalized edema formation. We believe that our mean is very close to the actual value. Our values are in essential agreement with those obtained by Schade,¹² Verney,¹⁸ Landis,¹⁶ and Muntwyler, Way, Binns and Myers¹⁸ and are much lower than those obtained by Stirling,¹⁰ Krogh,¹⁴ Govaerts¹⁵ and Kylin.¹⁷

We have determined the colloid osmotic pressure of normal dogs and have found it to average 18.5 mm Hg. The highest value was 21.7 and the lowest value 17.2 mm Hg (table 4).

TABLE IV
Colloid Osmotic Pressure Values in Normal Dogs

Date	Albumin	Globulin	Fibrinogen	Total Protein	Osmotic Pressure mm Hg at 37° C
2/3/31					21.7
8/17/31	3.49%	2.69%	41%	6.59%	18.0
9/15/31	4.81%	2.47%	43%	7.71%	17.9
9/18/31	4.56%	2.23%	65%	7.44%	18.8
9/19/31	4.90%	1.77%	58%	7.25%	19.6
9/30/31	3.61%	1.24%	45%	5.30%	17.3
10/6/31	3.8%	1.69%	44%	5.93%	17.2
10/26/31	4.67%	1.6%	49%	6.76%	21.2

Mean pressure 18.5 mm Hg

(These values are not corrected for the error due to the addition of sodium oxalate as the anti-coagulant.)

COLLOID OSMOTIC PRESSURE OF THE BLOOD PLASMA IN CASES OF NEPHROSIS AND NEPHRITIS

We²¹ have made 24 determinations of the colloid osmotic pressure in 14 cases of nephritis with edema (table 5). Whenever edema was present, the colloid osmotic pressure was always lower than 15 mm Hg, when the colloid osmotic pressure was 16 mm Hg or more, edema was absent or was being absorbed. The average colloid osmotic pressure for these edematous cases was 8 mm Hg. This value agrees well with the values obtained by Govaerts,¹⁵ Schade,¹² Fahr and Swanson,²² Muntwyler, Way, Binns and Myers¹⁸ and Kylin.¹⁷ The colloid osmotic pressure of one case of chronic nephritis in uremia without edema was found to be 27 mm Hg. This patient, however, had hypertension and we have found that in hypertension

the osmotic pressure of the plasma proteins tends to be slightly higher than normal

TABLE V
Colloid Osmotic Pressure in Cases of Nephritis with Edema

Date	Name	Albumin	Globulin	Fibrinogen	Total Prot	Osmotic Pressure mm Hg at 37° C	Edema
6/9/30	S M	95%?			3 69%	6 2	4+
6/13/30	S M					8 8	4+
6/18/30	S M					6 4	4+
6/23/30	S M					10 1	4+
8/11/30	S M					8 6	4+
9/29/30	D G					9 2	4+
4/14/31	D G					9 4	4+
8/11/31	D G	2 14%	1 76%	65%	4 55%	10 6	4+
10/10/31	D G	2 39%	2 19%	72%	5 29%	12 6	4+
10/30/30	B C					10 8	3+
7/18/30	F H					8 5	4+
10/1/30	F H					9 4	4+
10/7/30	E W					9 6	4+
10/22/30	O M					10 2	4+
8/7/31	M W	1 14%	1 63%	47%	3 25%	7 6	4+
12/27/32	E J					8 1	4+
2/8/32	E J					6 6	4+
1/2/33	M A B					8 1	4+
8/3/33	I C	2 38%	1 84%	65%	4 87%	8 8	4+
6/28/33	D P	1 28%	1 51%	40%	3 19%	6 6	4+
6/29/33	H N	1 08%	1 19%	68%	2 95%	7	4+
6/21/33	E V					10 6	4+
3/20/35	G L	2 51%	1 73%	61%	4 85%	10 3	3+

(These values are not corrected for the error due to the addition of sodium oxalate as the anti-coagulant)

THE EFFECT OF GUM ACACIA INJECTIONS ON NEPHROTIC EDEMA IN MAN

In order to demonstrate that the edema in nephrosis and nephritis was due merely to a reduced colloidal osmotic pressure in the plasma, we searched for some inert colloid which could be injected into the blood stream and which would have no other effect than to raise the colloid osmotic pressure. Hartmann²³ had shown that the intravenous injection of 30 per cent gum acacia in nephrotic patients led to a diuresis. Thirty per cent gum acacia solution has a colloid osmotic pressure many times higher than that of normal plasma. In fact, a 6 per cent gum acacia solution has approximately the same colloid osmotic pressure as normal plasma. Therefore it should be possible by injecting sufficient amounts of 30 per cent gum acacia to raise the colloid osmotic pressure to a point where edema would be absorbed. Referring back to our scheme of a capillary if we raise the colloid osmotic pressure sufficiently we should move the equilibrium point near the middle of the capillary and therefore have less transudation and more absorption. We have injected this solution into six patients with nephritis or nephrosis. In only three of these cases was it possible to inject enough gum acacia to produce the desired effect. However, when sufficient gum acacia could be

TABLE VI
The Effect of the Injection of Gum Acacia in a Case of Subacute Glomerulonephritis with Edema

Date	Weight	C c of 30% Gum Acacia	Intake	Output	Fluid Gain + or Loss -	NaCl in Urine		Colloid Osmotic Pressure	Acacia in 24 Hrs Urine
						%	Gm /24 Hrs		
1/25/33	171		400 cc	340 cc	60 cc +			on 1/2/33 = 8 mm Hg	
1/26/33			400 cc	550 cc	150 cc -				
1/27/33			400 cc	500 cc	100 cc -				
1/28/33		300 cc	615 cc	1875 cc	1260 cc -				
1/29/33		400 cc	750 cc	1950 cc	1250 cc -	62	9.55		7.38 Gm
1/30/33		300 cc	675 cc	2100 cc	1425 cc -	64	11.98		
1/31/33	134		400 cc	2750 cc	2350 cc -	55	13.8	Before acacia 12 mm Hg 1 hr after acacia 15 mm Hg	7.6 Gm
2/1/33			400 cc	2725 cc	2325 cc -	64	17.4		4.5 Gm
2/2/33	134		310 cc	1400 cc	1090 cc -	65	8.8	13 mm Hg	2.5 Gm
2/3/33			400 cc	1300 cc	900 cc -	47	5.85	12.6 mm Hg	69 Gm
2/4/33			495 cc	1150 cc	655 cc -	61	5.74		
2/5/33	126		450 cc	650 cc	200 cc -	64	4.1		93 Gm

injected without severe reactions marked diuresis followed. We shall give the results of only one of these experiments performed in a case of subacute glomerulonephritis with very marked edema (table 6). The colloid osmotic pressure was 8 mm Hg and the patient on an intake of 400 c c a day was barely maintaining her fluid balance. She was neither gaining nor losing edema. On the first day of the experiment she was given intravenously 300 c c of 30 per cent salt-free gum acacia furnished by the Eli Lilly Co. This day with an intake of 600 c c her output rose to 1900 c c, a loss of approximately 1300 c c of body fluid. The next day she was given 400 c c of gum acacia and again lost approximately 1300 c c of fluid. The third day she was given 300 c c gum acacia and lost approximately 1400 c c more fluid than she took in. On this third day the osmotic pressure of the plasma colloids was 12 mm Hg before the last injection of gum acacia, while after the injection the osmotic pressure was 15 mm Hg*. Several days later the osmotic pressure was still 13 mm Hg. The patient continued to put out large amounts of fluid. In a period of seven days she lost 11 liters of edema fluid with a corresponding loss in weight. The mere addition of an indifferent colloid to the blood plasma increased the total colloid osmotic pressure to a point at which fluid was drawn into the blood, carried to the kidneys and excreted as urine, thus producing a marked diuresis. During the time of this very marked diuresis of water there was also a very marked increase in the output of salt. At the height of the diuresis, the patient put out 17.4 gm of salt in one day on an intake of 2.5 gm of salt. In other words, this patient was putting out urine which contained nearly the same amount of salt as is present in normal tissue fluid. This tends to prove that the kidney is able to excrete salt very readily in nephrosis or nephritis with edema if the colloid osmotic pressure is raised sufficiently so that tissue fluid can be absorbed. These experiments also prove that the increase of the colloid osmotic pressure by some inert colloid not normally found in the blood is sufficient to cause an absorption of the edema with consequent excretion of water. The kidney itself has no difficulty in excreting water and salt if water and salt can be absorbed from the tissue spaces.

CONCLUSIONS

1 The edema fluid in nephritis, nephrosis and cardiac failure is a nearly pure ultrafiltrate of the blood plasma.

2 The formation of edema is for the most part a result of imbalance between the forces of capillary hydrostatic pressure and colloid osmotic pressure of the plasma. A substantial increase in capillary pressure or decrease in colloid osmotic pressure or a combination of both results in edema formation.

3 The method of Schade for the determination of the "onkotic" pres-

* Immediately after injecting gum acacia fluid is drawn into the blood, the plasma volume is increased and the colloids are diluted. Therefore the calculated colloid osmotic pressure is never attained.

sure is the logical method for the determination of the "effective" colloid osmotic pressure of the plasma because it measures the hydrostatic pressure at which ultrafiltration of the plasma salt and water just equals the reabsorption. For this reason in using this method it is unnecessary to calculate or measure the Donnan effect. The thermostatic control of temperature rules out any sudden thermometric effect during the measurement.

4 The normal colloid osmotic pressure of the plasma in man is approximately 21.4 ± 2.5 mm Hg.

5 The normal colloid osmotic pressure of the plasma in dogs is 18.5 mm Hg.

6 In nephrosis and nephritis with edema the colloid osmotic pressure is usually lower than 15 mm Hg and averages 8 mm Hg.

7 The injection of concentrated solutions of an inert colloid (gum acacia) increases the colloid osmotic pressure of the plasma and causes a disappearance of the edema with a corresponding diuresis of water and salt in the same proportions as they are found in edema fluid.

8 Retention of salt in nephritis is not due to renal insufficiency but is consequent to prerenal deviation in the ultrafiltrate or edema fluid.

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CUTANEOUS MANIFESTATIONS IN PSYCHOTIC AND PSYCHONEUROTIC INDIVIDUALS *

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IT is known that, as a result of their disorder, a small percentage of individuals with nervous or mental abnormalities develop habits which result in skin lesions, or even may become victims of constantly self-inflicted injuries to the skin or mucous membranes. These are cases of true dermatitis factitia. Some of these acts may be the result of a desire for attracting sympathy or attention to the individual, as in one of the cases mentioned recently by Klauder ¹ in which a hysterical woman systematically and secretly used lysol to produce extensive wheals or bands on her arms, which were exhibited to her acquaintances for their commiseration. Such cases are, however, merely behavior problems, although a mental or nervous disorder is responsible for the abnormal habit, it is not directly causative of the cutaneous lesion.

There appears to be a certain amount of evidence that in various psychoses, psychoneuroses and neuroses, in some types more than in others, there is a tendency to the development of more or less definite types of skin diseases, that is to say that, whatever may be the mode in which the effect is produced, these mental and nervous disorders are etiologic factors in the production of certain types of skin lesions.

The literature dealing with this subject is not voluminous, and, especially as regards the psychoses and psychoneuroses, is indefinite and lacking in clinical precision. I have, therefore, thought that it would be of interest to set down my personal clinical findings in the observation of a very considerable number of psychotic and psychoneurotic patients, in a definite percentage of whom skin lesions were observed, without there being, so far as could be observed, any other etiologic factor than the psychogenic one, further, to classify as far as possible the types of cutaneous lesions associated with definite psychogenic states and finally, to give the therapeutic result following a particular mode of treatment.

The data, which I have tried to make as complete as possible in regard to the clinical aspects, may, I hope, induce others, who have the opportunity, to make similar observations, with a view of verifying whether it is merely a conjecture or an established fact that psychogenic disorders are definite etiologic factors in cutaneous disorders, also, perhaps, to discover the mode of causation.

Theoretically, there are different ways in which nervous and mental disorders may affect the skin, especially its trophism. Of these perhaps

* Received for publication April 10, 1937

Permission granted by Chas M Griffith, Medical Director, U S Veterans Administration, Washington, D C

the most likely are the increased excitability and emotionality, acting probably on either or both the endocrine or other body secretions or the autonomic nervous system, particularly the trophic or sensory nerves supplying the nutrient vessels. Such factors are known to affect the skin in normal as well as in neurotic and psychotic subjects, but in psychotics especially the abnormal emotionality should be a particularly strong factor in producing effects upon the skin, although we are much in the dark in regard to the exact mechanism of such production.

A brief resume of the available literature will be in order before my personal contribution. It will be noted that the authors ^{giving} more attention to the effects of emotionality upon the skin in ^{red} give subjects than in psychotics or psychoneurotics.

Eller² was one of the first in this country, in 1929, to write on the subject of nervous and mental factors affecting the skin. He mentions as a recognized fact that the blood vessel tonus is regulated by several factors, among which may be included the psyche acting through the visceral nervous system, either the parasympathetic or sympathetic. These in turn may be influenced by the internal secretions. This vascular influence, of course, occurs in the skin as well as in other organs.

According to Eller, the skin conditions occurring in this group are (1) dermatitis factitia, (2) the compulsion neuroses, namely, dermato-thalassia, etc., (3) dermato-phobias, (4) emotional urticaria, (5) hysterical pemphigus, which is said to exist, (6) alopecia areata, lichen planus and certain eczemas of psychogenic origin.

Eller cited Strandberg who observed the frequent occurrence of vasomotor and trophic disturbances of the skin in insane persons, among which he included acrocyanosis, abnormal hair growth, anomalies of sweat secretion, trophic and other disturbances of the nails, etc., especially in patients with dementia praecox.

Bonjour,³ writing in 1929 upon the influence of the mind on the skin, cites Sack (of Baden-Baden) who expressed the belief that in certain psychogenetic phenomena the skin could be used as an organ of expression, especially if it had some pathologic disposition to act thus. Bonjour himself thought that warts, eczema and urticaria could be therapeutically influenced by suggestion, patients showing such lesions were persons whose nervous systems were affected either through emotions or through some other cause of excitement.

Joltrain⁴ states that "Emotional shock is always followed by a humoral disequilibrium—a hemoclastic crisis which is always followed by a series of phenomena. Herpes, dermatographism, etc. appear after strong emotions in those having such a disposition. Emotion can be considered as an antigen, as something which in a hypersensitive organism frees sensitizing substances."

Horan⁵ insists that the emotions acting through the endocrines and cir-

culatory systems can and do bring about many pathologic conditions of the skin

Stokes ⁶ of Philadelphia, writing in 1932, says "I have reached the belief that it is often impossible really to comprehend the urticarias of adult life, which are of more than two weeks' duration, without a genuine study of the personality problems involved" In an article published in 1930 Stokes and Pillsbury ⁷ stated "The larger our experience, the more careful our search, the more we are inclined to believe that in the urticarias and urticarial dermatitides of middle life, in the diathetic eczemas and rosacea, and even in dermatoses, which, like epidermatophytoses, seem far removed from psychologic considerations, the tension make-up, the personality defect, the conflict and anxiety, the repression and complex, have their place as causal influences" These writers considered that the mode in which the psychologic factor acts to produce urticaria was that emotion predisposed to acidity, acidity favored production of the gas bacillus, and the gas bacillus caused production of histamine and wheals on the skin

Crutchfield, ⁸ writing in 1932 upon the emotional and psychic factors in skin disease, classes these types of skin lesions in four groups

- 1 Those in which there is some definite organic pathologic lesion in the sensory or trophic nerve,

- 2 Those conditions which are a result of pathologic changes in the peripheral nerves (trophic ulcers, gangrene),

- 3 Those conditions in which no known pathologic lesions exist in the nervous system but in which skin lesions are pronounced

- 4 Disturbances in the autonomic nervous system This is the group in which emotions play the most important part

There is a less definite class composed of skin diseases which cannot be placed in any anatomic group but which are produced by the emotions of the patient These may be aggravated, prolonged or become incurable due entirely to the mental reactions of the patients

Klauder ¹ has just published an article on the psychogenic aspects of skin diseases He gives a long list of such lesions which, besides those of a circulatory or sensory nerve origin, includes stigmata, trichotillomania, angiospasm, etc He mentions anesthetic areas observed in hysterical patients, also, that psychoneurotics have a peculiar lability of the vasomotor apparatus manifested in disorders of the peripheral circulation Peripheral circulatory disturbances in psychopathy are stressed Klauder thinks that dermatographism of psychoneurotics is closely related with angioneurotic edema, urticaria and frank dermatitis or acute eczema Further, that cutaneous phenomena, characterized by vascular dilatation, erythema and exudation, when appearing and disappearing suddenly are suggestive of psychic or allergic causation

My personal observations refer to skin lesions noted in psychotic and psychoneurotic individuals for which no other etiologic factors could be

found apart from the nervous or mental disturbance. A total of 1350 such patients was observed. The average age was 44 years, the minimum, 38 years. Of this total group, 150 patients were classed as psychoneurotics, and of these 27 (18 per cent) showed or developed skin lesions during the period of treatment, 1200 patients were classed as psychotics and, in these, 76 cases (6.33 per cent) of skin diseases were observed or developed during the period of treatment.

TABLE I
Percentage of Skin Diseases in Sub-Groups of Psychoneuroses
150 Cases (11% of total patients observed)

Sub-group	No Cases Skin Lesion Observed	Percentage of Psychoneurosis Group
Hysterical	14	9 $\frac{1}{3}$ %
Anxiety state	9	6%
Psychasthenia	4	2 $\frac{3}{5}$ %
TOTAL	27	18%

Table 1 gives the percentage of each psychopathologic sub-group for the psychoneurotic cases and the total percentage of skin lesion cases observed in each sub-group.

TABLE II
Types of Skin Diseases Accompanying Psychoneuroses

TYPE	SUB-TYPE	No of patients in group	TYPE OF SKIN DISEASES	No. in group under treatment	Recovered	Improved	Unchanged	REMARKS
PSYCHONEUROSIS	HYSTERICAL TYPE	14	Acne vulgaris	8	2*	1	5	*Skin lesions cleared up and remained symptom free for over nine months *Suffered a relapse whenever treatment was discontinued *Improved also in general health—mentally and physically
			Herpes zoster	4	0	3*	1	
			Seborrheic dermatitis	2	0	1*	1	
	ANXIETY STATE	9	Acne vulgaris	5	2	1	2	This entire group improved in general health
			Eczemas of undetermined origin	3	0	1	2	
			Dermatitis factitia	1	0	1	0	
	PSYCHAS- THENIA	4	Impetigo	2	0	1	1	*Skin lesions cleared up after 2 $\frac{1}{2}$ months of treatment
			Seborrheic dermatitis	1	0	1	0	
			Urticaria	1	1*	0	0	

"Recovered" as here used indicates that the manifestation did not recur for a period of three months.

Table 2 gives the types of skin lesions observed in the foregoing psychoneurotic sub-groups with the result of treatment.

PSYCHOTIC AND PSYCHONEUROTIC INDIVIDUALS

TABLE III

Percentage of Skin Disease in Sub-Groups of Psychoses

PSYCHOSIS

1200 Cases or 89% of Total Patients Observed

Sub-group	No Cases Skin Lesion Observed	Perce Psy C
Dementia praecox	49	4
Manic depressive	16	1
Psychopathic personality	6	
Psychosis with mental deficiency	3	
Miscellaneous undiagnosed psychosis	2	
TOTAL	76	6

Table 3 gives the percentage of each psycho-pathologic sub-group in 1200 psychotic cases and the percentage of skin lesions observed in each group

TABLE IV

Types of Skin Diseases Accompanying Psychoses

TYPE	SUB-TYPE	No of patients in group	TYPE OF SKIN DISEASE	No in group under treatment	Recovered	Improved	Unchanged	REMARKS
Dementia Praecox	SIMPLE	8	Acne vulgaris	4	1	2	1	
			Follicular eruption of the trunk and extremities	2	1	0	1	
			Herpes zoster	1	0	1	0	
			Psoriasis with infiltrated patches	1	0	1	0	
	HERBEPHENIC	20	Eczemas of undetermined origin	8	0	3*	5	*Edematous lesion quite unexpected in treatment
			Herpes zoster	2	0	1	1	
			Ichthyosis	2	0	2	0	
			Seborrheic dermatitis	6	1	2	3	
			Pellagra	1	1*	0	0	*Dietary restriction served in addition
			Pruritus	1	0	1	0	

TABLE IV—*Continued*

TYPE	SUB-TYPE	No of patients in group	TYPE OF SKIN DISEASE	No in group under treatment				REMARKS
					Recovered	Improved	Unchanged	
MANIC DEPRESSIVE	MANIC	6	Urticaria Seborrheic dermatitis	5 1	0 0	1 1	4 0	
	DE- PRESSED	8	Acne vulgaris Herpes zoster Psoriasis with infiltrated patches Eczema	5 1 1 1	1 0 0 0	2 1 1 1	2 0 0 0	
	INVOL MELANCHOLY	2	Urticaria	2	0	2	0	Improved in general mental and physical condition while on treatment
	PSYCHOPATHIC PERSONALITY	6	Dermatitis factitia Herpes zoster Acne vulgaris	3 2 1	0 0 1	2 1 0	1 1 0	
	PSYCHOSIS WITH MENTAL DEFICIENCY	3	Seborrheic dermatitis Fungus infection of scalp	2 1	0 0	1 1	1 0	
	MISC UNDIAG- NOSED PSYCHOSIS	2	Ichthyosis hystrix Eczema of undetermined origin	1 1	0 0	1 1	0 0	Clinical improvement in me- tabolism and gastrointestinal functions, also mentally

"Recovered" as here used indicates that the manifestation did not recur for a period of three months

Table 4 gives the types of skin lesions observed in the psychopathic sub-groups with the psychotic sub-groups, and the result of treatment

Table 5 gives a comparison of the results of treatments of skin lesions in the two main groups

TABLE V

Comparative Response to Treatment of Skin Diseases in Psychoneurotic and Psychotic Cases
Total Number of Cases Observed = 1350

PSYCHONEUROSIS 150 Cases = 11% of Total	Cases in which skin lesions developed 27 Cases or 18% of Group	Recovered = Five or 18%
		Improved = Ten or 37%
		Unchanged = Twelve or 44%
PSYCHOSIS 1200 Cases = 89% of Total	Cases in which skin lesions were not observed 123 Cases or 82% of Group	
PSYCHOSIS 1200 Cases = 89% of Total	Cases in which skin lesions developed 76 Cases or 6 $\frac{1}{3}$ % of Group	Recovered = Nine or 11 $\frac{1}{3}$ %
		Improved = Thirty-two or 42%
		Unchanged = Thirty-five or 46%
PSYCHOSIS 1200 Cases = 89% of Total	Cases in which skin lesions were not observed 1124 Cases or 93 $\frac{2}{3}$ % of Group	

The skin lesions which were observed in the two groups were as follows

Acne vulgaris
Dermatitis factitia
Pellagra with characteristic facies, pigmentation and exfoliation
Parapsoriasis lichenoides
Psoriasis with deeply infiltrated patches
Ichthyosis hystrix
Herpes zoster
Dermatophobias
Seborrheic dermatitis
Pruritus
Eczemas of undetermined origin

Studies of urine, blood, and basal metabolic rate were made routinely. The urine showed no significant departure from normal. Blood cholesterol was within normal limits in most of the patients. The fasting blood sugar was normal. The basal metabolic rate varied between minus 24 and plus 20. In this group of cases the schizophrenics had the lowest basal metabolic rate. None of these patients, regardless of the metabolic rate, showed any signs of disturbed thyroid function.

Roentgen-rays of the pituitary region showed normal size of the sella turcica without erosion in practically all the cases so studied. One case showed an abnormally large sella but without evidence of erosion.

Treatment of these psychotic and psychoneurotic patients with skin lesions consisted of the administration of U S P standardized thyroid in tablets, in doses from $\frac{1}{4}$ to 3 grains per day, and of injections of $\frac{1}{2}$ c c of antuitrin every other day. The dosages were varied to some extent according to the level of the basal metabolic rate, the pulse, weight, skin lesions and the degree of mental disturbances.

The response to this treatment was more favorable in psychoneurotic than in the psychotic group (table 5). In cases in which improvement took place the change was noted after three or four months of treatment (tables 2 to 4).

The use of this form of therapy was largely empirical. It was suggested by the frequency of endocrine disturbances associated with psychosis or psychoneurosis. The results obtained are not considered decisive.

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AN ANALYSIS OF 62 CASES OF PRIMARY CARCINOMA OF THE LIVER BASED ON 24,400 NECROPSIES AT BELLEVUE HOSPITAL *

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THE material for this study of primary carcinoma of the liver was derived from 24,400 consecutive autopsies performed at Bellevue Hospital from 1906 to 1936. In selecting these 62 cases a review of all cases included in our protocols as primary carcinomata of the liver was carried out. Those cases which, either on analysis of the protocols, or, microscopically, did not represent typical examples of carcinoma, were excluded, together with those in which clinical records or microscopic preparations were not available. All cases were likewise excluded in which duct cell carcinoma of the pancreas was suspected, microscopically or otherwise.

In this presentation the classification and diagnostic criteria laid down by Egge¹ are adhered to. Those cases with invasion or destruction, or with metastases, or with neoplastic thrombus formation, visible either grossly or microscopically, or both, are termed carcinoma.

Macroscopically three groups are considered

- 1 The nodular form, in which the neoplastic growth is represented by discrete nodules, varying in size from a few millimeters to several centimeters. These nodules may involve one or more lobes.
- 2 The massive form, in which there is one massive nodule occupying an entire lobe, usually the right. There may be numerous smaller tumor nodules in adjacent liver tissue. This form frequently merges with that of group 1.
- 3 A diffuse form in which it is impracticable to differentiate carcinoma from cirrhosis of the liver, except microscopically.

Microscopically, the differentiation between the primary liver cell and bile duct types is considered. Cases occur in which a differential diagnosis is difficult or impossible to make because of varying pictures in different parts of the tumor growth. These are included under a separate heading, namely, indeterminate or dual origin. According to this microscopic classification, 39 of the Bellevue Hospital cases are of liver cell type, 21 of bile duct type, and 2 of indeterminate or dual origin. These figures are presented at this point in anticipation of further analysis which depends on this division.

No individual survey has heretofore been made of so large a group. Hale-White² analyzed 25 cases occurring in 18,500 necropsies, an incidence of 0.13 per cent. McIndoe and Counseller³ analyzed 62 cases collected from 42,276 necropsies, an incidence of 0.14 per cent. The limits of varia-

* Received for publication June 10, 1937.

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tion of incidence extend from 0.08 per cent by McIndoe and Counsellor in their own cases, to 0.33 per cent by Von Glahn and Lamb⁴ and Fried⁵. In the present analysis the incidence was found to be 0.25 per cent, or one case of primary carcinoma of the liver in every 394 necropsies.

The sex incidence in the 62 cases at Bellevue Hospital was 53 males and 9 females. However, accurate figures on the number of necropsies in males and females were not obtainable, the approximate ratio being three males to one female, thus giving a corrected incidence of 18 males to 9 females. Eight of the nine cases in females were in the bile-duct group and one in the liver cell group. The significance of this is not clear. Are the possible underlying etiological factors of significance? Does the predominance of cirrhosis of the liver in males play a rôle? No definite answer to these questions is available as yet.

In the Bellevue Hospital series 53 cases occurred in the white race, 4 in negroes, and 5 in the yellow race (4 Chinese and 1 Japanese). These latter figures comprise 6.4 per cent and 8.1 per cent, respectively, of the present series.

The incidence in negroes parallels the admission rate of that race to Bellevue Hospital. That of the yellow race, however, is much higher than the admission rate. Strong and Pitts⁶ of Vancouver, where the Chinese populace is relatively larger than that of New York City, reported a higher incidence of primary carcinoma of the liver in the yellow race. They reported nine cases of primary carcinoma of the liver occurring in 1024 necropsies. Of the 9 cases eight were in Chinese. The number of necropsies on Chinese in their series was 115, making an incidence of 6.9 per cent in Chinese as compared with 1 case in 909 necropsies in white people, or an incidence of 0.11 per cent.

The yearly percentage incidence in the autopsy series of primary carcinoma of the liver including both liver cell and bile duct origin has shown great variation over the course of years from which this series is taken. No definite trend towards an increasing or decreasing incidence is determinable from our figures.

The average age incidence in the Bellevue Hospital series was 52.5 years—that of the liver cell type 51.2 years, and that of the bile duct type 54.8 years, no cases occurred in children. Classed according to decades the highest incidence is in the fifth, sixth and seventh decades, as shown in the following table.

TABLE I

Age Incidence	Liver Cell	Bile Duct	Dual Origin
30-39	3	3	
40-49	12	6	
50-59	14	4	
60-69	8	7	2
70-79	1	0	
80-89	1	1	

ANALYSIS OF CLINICAL HISTORY AND PHYSICAL FINDINGS

Clinically, it is impossible to distribute these cases into their respective anatomical groups. An attempt has been made to classify them clinically into one of the following six groups

- 1 Those cases presenting chiefly history and symptomatology of cirrhosis of the liver. This group comprises the largest number (18)
- 2 Those cases presenting chiefly history and symptomatology of disorders of biliary or gastrointestinal tracts. This group comprises the second largest group (14)
- 3 The third group comprises those cases which present signs of a malignant growth at some site in the body characterized, clinically, by loss of weight, weakness, appearance of metastatic nodules elsewhere, etc. In this group are 14 cases, four of which were diagnosed clinically as primary carcinoma of the liver
- 4 Those patients who enter the hospital on the surgical services and die before or shortly after intervention due to spontaneous hemorrhage from a ruptured carcinomatous nodule of the liver. There are three cases in this group
- 5 Those patients whose symptoms and signs do not point to pathological changes in the liver. There are six cases in this group
- 6 Those patients dying before any diagnosis is possible. In this group are seven cases

Many of the cases in one group merge with cases of other groups. This fact explains the difficulty in formulating a clinical picture for a disease which is so variable in its symptomatology.

The majority of these patients entered the hospital with complaints either directly or indirectly referable to the liver. The following analysis shows the variety of complaints together with the average duration of each

Complaint	Number of Cases	Average Duration of
Vague gastrointestinal symptoms such as dyspepsia, anorexia, occasional vomiting, etc	20	6 weeks
Ascites	19	9 weeks
Right upper quadrant pain	16	6 weeks
Weakness	10	2 months
Jaundice	9	4 weeks
Edema (dependent)	5	4 weeks (all in liver cell type)
Loss of weight	5	Unknown
Dyspnea	4	Indefinite
General abdominal pain	3	24 hrs or less
Fever	2	1 week
Diarrhea	1	7 weeks
Hematemesis	1	1 day
Metastatic foci		
Enlarged nodes of neck	1	1 month
Chest pain	5	1 month
Ulcer of eye	1	6 months

The usual case had two or three major complaints. However, patients with vague gastrointestinal symptoms, right upper quadrant pain (fre-

quently simulating that of cholecystitis) and rapidly accumulating ascites comprise the largest group of cases. Loss of weight as a symptom plays an apparently minor rôle, having been mentioned in only five cases. This may be explained on the basis of the counteracting gain of weight due to ascitic accumulation. Several patients sought medical attention because friends noticed their rapidly increasing girth. Rolleston⁷ reports that two of his patients gained weight. This might well be explained on the basis of ascites. Edema, especially of the dependent sort, was complained of in only five cases, although it was found more frequently on physical examination. It usually appears late in cases of primary carcinoma of the liver and is of differential significance in those patients with complaints referable to cardiac decompensation. Often, it may be difficult to separate the symptomatology of one from the other. This was true in three of the above patients. Fever as a chief complaint was present in two cases only, one in each type of carcinoma. This will be considered in greater detail under clinical findings. Hematemesis occurred once only as did diarrhea. The former fact is of interest because of its higher incidence in uncomplicated cirrhosis of the liver. In primary carcinoma of the liver, the course, as will be emphasized, is much shorter from the onset of symptoms to exitus than is that of cirrhosis of the liver. Collateral circulation is not as well established, therefore, as it is in cirrhosis of the liver.

COURSE

The average course from onset of symptoms to death was 3.2 months. Taken individually, that for the liver cell type was 2.5 months, that for the bile duct type 4.17 months. In ten cases the course was not ascertainable. These figures are unsatisfactory. No definite point of onset of the carcinomatous transformation could be ascertained. In many patients symptoms were masked or so negligible that they were not mentioned. Having no definite point of inception of the malignant process to compute from, the known time of onset of the more severe complaints was used as the criterion from which to estimate the onset of the disease. However, one does learn from these figures that the duration of the illness from the onset of symptoms to death is a short one, more so in the liver cell type than in the bile duct type. The extent of liver involvement seems to be correlated with the length of life. Those patients who show less extensive involvement of the liver pursue a somewhat longer course, as do those in whom the cirrhotic process in the liver is less severe.

ETIOLOGY

Karsner,⁸ reviewing nine cases clinically and pathologically, considered several factors as possible contributing causes, among which were alcohol, tobacco and opiates. Syphilis was not mentioned in any of his cases. In the present analysis it was impossible to consider all these factors inasmuch

as reference to many of them was not made. However, syphilis and alcohol were mentioned either in the affirmative or negative in the majority of instances.

In ten cases of the present series, nine of which were of the liver cell type, indications of syphilis were present, such as positive Wassermann reactions, positive histories and affirmative postmortem findings. In 22 patients a history of overindulgence in alcohol was obtained. Nine were heavy drinkers either in the past or at the time of admission. The remainder of the 22 patients fell in the class of moderate drinkers. In ten cases no information was available on this point. Here also the evaluation can readily be seen to be extremely difficult because of the personal equation involved. The distribution of the cell types was approximately equal. No notation on any of the above cases was made as to the incidence of pellagra, peripheral neuritis or beriberi.

The physical findings varied greatly. In some instances no physical changes referable to carcinoma of the liver were detectable. In others, the findings were more indicative of pathological changes in the liver.

General Appearance In spite of the absence of loss of weight in the majority of the patients, emaciation or signs of poor nutrition were recorded in the greater percentage.

Jaundice Jaundice was present in 32 patients, or in 51.6 per cent, at some time during their hospitalization. It was usually mild in type. There was a noticeably higher incidence of jaundice in the bile duct than in the liver cell type, 57.1 per cent in the former, 46.1 per cent in the latter. This, compared with the incidence of jaundice in cirrhosis of the liver, is higher, that in cirrhosis being less than 30 per cent of all cases at some time in their course, and then usually slight and frequently transient. Jaundice was relatively infrequent in the massive type of primary carcinoma. The reasons for this will be evident after consideration of the naked eye pathological changes.

Ascites Ascites was present in 28 cases, or in 45.2 per cent. The incidence was about equal in both the bile duct and liver cell types.

Hepatomegaly The percentage of patients in whom the liver was either palpable or enlarged on percussion was 70.0 per cent, or in 44 cases. In a large number of patients the presence or absence of nodularity was difficult to determine because of ascites. However, it was mentioned in 28 of the 44 cases. The liver was tender in only five cases. Rolleston states that as a rule, patients with cirrhosis of the liver and carcinoma complain oftener of tenderness than those without carcinoma. This statement is not borne out in the present series where the liver was tender in a minority of patients. Patients with carcinoma complained of pain more frequently, usually located in the right upper quadrant, than those with portal cirrhosis alone. This fact has been mentioned by several writers.

Splenomegaly The spleen was palpable in one case only. This in part was probably due to interference by ascitic accumulation.

Dependent edema was present in eight cases. In all of them there was ascites as well.

Hemoglobin determinations and red blood counts were done in 20 cases. The average in these cases was 73 per cent hemoglobin with 3.41 million red blood cells, the extremes varying from 49 to 96 per cent hemoglobin and 2.51 to 5.1 million red cells. White blood counts were done in 25 cases, the average count being 10,920, the extremes varying from 7000 to 21,800. Icteric indices were done in several cases but no conclusions appear to be justifiable in so small a number of determinations.

Temperature. Fever was observed in 29 cases. This, as a rule, was mild, varying from 99 to 101 degrees Fahrenheit. In four patients in whom the temperature reached a higher level, clinical signs of pneumonia were present. In short, fever was present in 25 patients in whom no findings referable to infection or other source of fever were found. This constitutes 47.3 per cent, inasmuch as nine cases ran no clinical course. This figure is somewhat lower than that reported by others.

PATHOLOGY

Classification. The gross pathological changes in the liver comprise, first, those of the tumor itself and second, those of the associated cirrhosis, when present. According to the classification of Eggel, the 62 cases in this series fall into the three groups as follows:

Massive type	13 cases, nine of which were of liver cell and four of bile duct origin.
Multinodular type	37 cases, 23 of which were of liver cell, 12 of bile duct, and two of dual origin.
Diffuse type	12 cases, six of which were of liver cell and six of bile duct origin.

The above figures show the preponderance of the multinodular type over the combined diffuse and massive types. A still larger number of cases, however, might well have been classified as of the massive type had it not been for the fact that many small secondary nodules were present in the left lobe of the liver.

Cirrhosis of the Liver. The association of cirrhosis of the liver in these cases is frequent. Eggel reports an incidence of 85 per cent of cirrhosis of the liver in primary liver cell carcinoma, and 59 per cent in the bile duct type. Karsner reports cirrhosis in the nine cases studied by him, four of which were of liver cell origin, and five of bile duct origin. In the present series many cases were diagnosed by the naked eye as combining primary carcinoma and cirrhosis of the liver. However, on microscopic examination several fallacies became apparent. First, as mentioned by Eggel, is the desmoplastic reaction to the tumor growth that is present in both forms, although it is more severe in the bile duct type. In order to ascertain the presence or absence of cirrhosis, one must take sections far enough from the tumor tissue in order to exclude desmoplastic reaction. Second, the

pressure of tumor nodules, together with necrosis of surrounding tissue and subsequent fibroblastic reaction, must be considered in determining the presence of a cirrhotic process. One must examine uninvolved tissue to exclude these factors. Third, biliary obstruction due to tumor encroachment on bile radicles frequently causes fibrosis of liver tissue. In such situations, however, the fibrosis is usually biliary in origin rather than portal.

With the above facts in mind, an attempt was made to ascertain the incidence of cirrhosis of the liver in the present series. In some instances it was impossible to make this decision because of the presence of tumor tissue throughout the liver. These cases were usually of the multinodular type. They were six in number. It was found that 25 of the 39 cases of carcinoma of the liver cell type, or 64.1 per cent, were attended by some degree of cirrhosis, while only seven of 21 cases of bile duct origin, or 33.3 per cent revealed detectable cirrhosis. These figures are somewhat lower than those of Eggel's. His cases, however, were collected in greater part from different sources, and many of them were classified without benefit of microscopic examination.

Microscopic Types of Carcinoma As already mentioned, there are three microscopic types of primary carcinoma of the liver—the liver cell, bile duct and dual or indeterminate.

The liver cell type of carcinoma is composed of strands and cords of large polygonal cells with pinkish cytoplasm and large round vesicular nuclei frequently having one or two nucleoli. These cells are arranged in cords and may even simulate lobules of liver tissue. The cells at the edges of the tumor nodules may frequently be traced in the process of transition from apparently normal liver cells. No central veins are discernible in these tumor nodules, but bile is often present in the intercellular spaces and in the accompanying biliary radicles which, in some instances, show marked proliferation. The formation of giant cells by amitotic division is frequent. There are usually moderate or even marked signs of anaplasia, characterized by variations in the size and shape of the cells as well as in their staining properties. In the majority of these cases tumor invasion of the veins and lymphatics may be detected microscopically.

The bile duct type of tumor, in contrast to the liver cell type, assumes the appearance of an adenocarcinoma, the lining cells varying from low cuboidal to tall columnar, depending on their origin from the smaller or larger biliary radicles. The cytoplasm is usually clear, somewhat basophilic, with round or oval, hyperchromatic nuclei. Nucleoli and giant cells are much less frequent than in the liver cell type. At times the structure of the tumor may vary from simple bile duct proliferation to that of a true adenocarcinoma. There is a more marked desmoplastic reaction in the bile duct than in the liver cell type. As in the liver cell type there is evidence of invasion of veins and lymphatics by tumor tissue.

In both types there is usually moderate lymphocytic reaction in the stroma. This is pronounced in cases associated with cirrhosis of the liver.

The dual or indeterminate type is rare. The fact that in this type differentiation is so irregular suggests a higher degree of malignancy as far as microscopic evidence may be depended upon to estimate the degree of malignancy of any tumor. However, with only two cases from which to draw conclusions, little can be said on this point with any measure of certainty. Both cases in question, however, metastasized to the lungs. This fact supports the view that tumors of dual origin tend in the direction of a somewhat exalted degree of malignancy.

Hemochromatosis No figures on the incidence of hemochromatosis in primary carcinoma of the liver are available. In the present series there were encountered six cases, or an incidence of 9.9 per cent. In all six cases there was an associated cirrhosis of the liver. However, there were only a total of 32 cases in the 62 cases of this series which had cirrhosis of the liver. This, therefore, would give an incidence of 18.7 per cent of hemochromatosis in those cases of primary carcinoma of the liver associated with cirrhosis. The incidence is noticeably higher than that of hemochromatosis in cirrhosis of the liver without primary carcinoma which has been variously reported as occurring in 7 to 10 per cent of all such cases.

Size of Liver The size of the liver was mentioned in 48 of the 62 cases of primary carcinoma in this series. The average was 2900 grams. In four the liver was mentioned as "normal" or "small", in eight as "large" and in one case no mention was made of the size. The average size of the liver in 30 cases of the liver cell type was 2834 grams, while that in 17 cases of the bile duct type was 2990 grams.

Ascites Ascites was present in 45 cases, or in 72.6 per cent—the most constant finding of the series. This varied in amount, averaging three to four liters. The ascites was bloody in six cases, two of which showed superficial necrosis of tumor nodules with rupture and hemorrhage. In seven others ascites was serosanguinous in character.

Splenomegaly Splenomegaly was present in the majority of cases. In 39 of the 62 cases where the weight was mentioned, the average was 354 grams, and was slightly higher in the bile duct type. In 13 cases the spleen was mentioned as "normal" in size, while in six it was "enlarged". No mention of size was made in four cases. It has been said that the incidence of splenomegaly is in direct proportion to that of neoplastic thrombosis of the portal or splenic veins. In 27 cases of the liver cell type analyzed in this paper, the average weight of the spleen was 331 grams. Of these, 11 showed neoplastic venous thrombosis, 10 involving the portal vein (and, in three of them, the splenic vein as well), and in one case intrahepatic venous channels. Sixteen had no naked eye evidence of thrombosis. In one of the 11 cases with venous thrombosis, the spleen weighed 90 grams. In the others it weighed over 150 grams. In 12 cases of the bile duct type the

average weight of the spleen was 380 grams. Neoplastic venous thrombosis was mentioned in three and in all of them the spleen weighed over 150 grams. The heaviest spleen in the entire series weighed 900 grams and showed no naked eye evidence of tumor thrombosis of any part of the portal system. The explanation of the splenomegaly on the basis of portal obstruction is supported by the fact that, on microscopic examination in the majority of cases, venous invasion was evident. This, together with the degree of portal cirrhosis, explains the higher incidence of splenomegaly and ascites in carcinoma than in cirrhosis of the liver alone.

Jaundice The incidence of jaundice was the same clinically and post mortem. Jaundice was explainable in the majority of cases on the basis of biliary obstruction by pressure from tumor nodules. This point is borne out by the infrequency of jaundice in cases of the massive type, that is to say, those which were not attended by secondary nodules. In other instances jaundice was due to widespread destruction of liver tissue by tumor growth.

Metastases The secondary spread of primary carcinoma of the liver takes place by direct extension and by metastasis through the blood and lymph channels. Solitary distant metastases to brain, bone, kidney, etc., are not uncommon. In 19 cases, or in 30.6 per cent, naked eye evidence of neoplastic venous thrombosis was present. In several cases this process involved two or more of the larger venous channels leading to or from the liver. In six of the 19 cases there were visceral metastases likewise visible to the naked eye. The tumor thrombi were not adherent to the wall of the vessel but were composed of organized and laminated blood clot in which were strands and masses of tumor tissue. In two cases, tumor thrombi were found to have travelled through the inferior vena cava into the right auricle of the heart. In several, the splenic vein was thrombosed throughout its entire length. In 29 cases, or in 46.8 per cent of the entire series, there was no naked eye evidence of metastasis. In the remaining 33 the sites of metastases were numerous. The most frequent were the periportal lymph nodes and the lungs, especially the right lung. The reason for this is evident when one appreciates the frequency of venous and lymphatic invasion by these tumors. On the contrary, it is amazing that so many cases exhibit freedom from metastases in spite of the high incidence of venous and lymphatic neoplastic invasion.

The following table shows the sites of metastases in both types.

In connection with the general subject of metastasis in primary carcinomata of the liver, it is interesting to note that Bolker⁹ and his associates recently reviewed the literature with especial reference to the occurrence of bone metastases. They found only nine such cases recorded. In the present series three examples of metastasis to bone were noted. In one case the metastases were multiple and involved ribs, vertebrae and the left orbital bone, in the other two ribs alone were involved. In another case of this series the spleen was invaded by retrograde growth through the splenic

	Liver Cell Type	Bile Duct Type	Total
Lung	9	5	14
Pleura	2	1	3
Lymph nodes			
Hilar (portal)	6	3	9
Mesenteric	5	1	6
Mediastinal	0	2	2
Inguinal	1	0	1
Cervical	2	0	2
Omentum	1	0	1
Kidney	2	0	2
Adrenal	1	2	3
Pancreas	2	1	3
Stomach	1	1	2
Peritoneum	1	2	3
Heart muscle	0	1	1
Bone			
Ribs	3	0	3
Vertebra	1	0	1
Orbital bones	1	0	1
Spleen	1	0	1
Eye	1	0	1

vein The size of the spleen was not mentioned Involvement of the heart muscle occurred once by direct extension through the pericardium from a metastasized mediastinal node

COMMENT

Only seven of the above 62 cases were diagnosed clinically The diagnoses entertained in order of frequency were (1) carcinoma of the stomach with metastasis to the liver, (2) cirrhosis of the liver, (3) carcinoma of the head of the pancreas, (4) "malignancy" of the liver, primary site undetermined, (5) cardiac decompensation In the remaining 55 cases there is no available data to show that the possibility of primary carcinoma of the liver was even suggested It would seem that the diagnosis should be made more often if its relative frequency is borne in mind Symmers, at Bellevue Hospital, correlating 20 years' experience in the necropsy rooms and in the wards, has successfully made the clinical diagnosis in seven instances based on the following criteria

- (1) A male patient over thirty-five years of age
- (2) A large palpable tumor mass in the right lobe of the liver
- (3) No primary tumor discoverable elsewhere
- (4) Jaundice, usually mild
- (5) Ascites
- (6) An otherwise unexplainable fever of mild degree

It was found that each of the 62 cases fulfilled at least four of the above criteria and in the majority of cases five or even all of them The author believes that a history of either vague gastrointestinal nature of short dura-

tion or signs of portal obstruction in the form of rapidly accumulating ascites should be used as additional information

The history of rapidly accumulating ascites in primary carcinoma of the liver is in contra-distinction to that of ascites due to other causes—cardiac failure, tuberculosis or carcinomatosis of the peritoneum, etc. In ascites of cardiac origin evidence of its cause is practically always available. In ascites of peritoneal origin due to carcinoma, tuberculosis or the like, findings indicative of its cause are likewise apt to present themselves. On the other hand rapidly accumulating ascites may be due to thrombosis of the portal vein of variable origin. In this connection it is to be recalled that neoplastic thrombosis of the portal vein not infrequently occurs in association with primary carcinoma of the liver

SUMMARY AND CONCLUSIONS

1 Primary carcinoma of the liver, formerly regarded almost in the light of a curiosity, is shown in this paper to occur once in every 394 necropsies, an incidence of 0.25 per cent based on 24,400 consecutive necropsies performed at Bellevue Hospital over an unbroken period of 30 years. The Bellevue series consists of 62 cases, in every one of which the diagnosis was verified by microscopic examination. It is believed to be the largest series thus far derived from a common source

2 Primary carcinoma of the liver is a clinical and pathological entity susceptible of diagnosis during life

3 The clinical diagnosis may be postulated with reasonable certainty on the following criteria (Symmers) (a) the presence of a palpable massive solitary growth in the right lobe of the liver in a male over 35 years of age, (b) inability to determine a primary growth in any other part of the body, (c) jaundice, usually of a mild grade, (d) ascites and (e) a low degree of otherwise unexplainable fever. In addition to these criteria a preliminary history of vague gastrointestinal disturbances of short duration or signs of portal obstruction extending over a period of a few weeks only, should likewise be taken into consideration (Gustafson). Clinically, the disease pursues a rapid course, death occurring, as a rule, within three to four months after the onset of detectable symptoms and signs

4 In the Bellevue series of 62 cases of primary carcinoma of the liver, 32, or 51.6 per cent were associated with cirrhosis of the liver, including six cases of hemochromatosis of the liver with cirrhosis

5 Microscopically, 39 of the 62 cases studied at Bellevue Hospital were obviously derived from the liver cells and 21 from the bile ducts, 2 were of indeterminate or dual origin. The liver cell type is characteristic. It has multiple points of origin and its cell constituents may be traced directly into neighboring apparently normal parenchyma cells. The bile duct type, as should be expected, is histologically indistinguishable from the duct cell carcinoma of the pancreas

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THE CLINICAL USE OF CRYSTALLINE INSULIN *

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SINCE the discovery of insulin by Banting and Best,¹ unremitting effort has been put forth toward the improvement of the product. One of the lines of endeavor has been to make insulin purer by crystallization.

Insulin was first crystallized by Abel^{2, 3, 4} in 1926. He prepared it from highly purified commercial preparations. Howard and DeLawder⁵ were the first to determine whether this crystalline insulin could be used therapeutically in human beings for the treatment of diabetes mellitus. Four diabetic patients were carefully regulated on diets and standard insulin, then crystalline insulin was substituted for standard in equivalent doses. They observed no appreciable difference except for a slight increase in carbohydrate tolerance which they thought could be expected in diabetic patients under treatment.

Until recently crystalline insulin was not used clinically because the yield of this insulin was small and it was therefore not commercially practical. In February of 1936, however, a new method of crystallizing insulin was developed by Dr. Melville Sahyun, of Detroit, which was practical for commercial use. We had the opportunity of making clinical trials of this crystalline insulin and found it to be suitable for the treatment of diabetes.⁶

Comparative studies were then made of standard commercial and of crystalline insulin. These studies were conducted with 20 patients and the conclusions were that crystalline insulin could be used in the treatment of diabetes mellitus and that with its use the blood sugar levels could be controlled with fewer doses and fewer units of insulin than was the case with standard insulin. Freund and Adler,⁷ Mains and McMullen,⁸ and Barach⁹ have reported similar results.

During the past year we have used crystalline insulin in the treatment of 100 diabetic patients who range in age from six to 86 years and who present a variety of complications. Some of these patients were being treated in the hospital as in-patients, some were treated in the clinic as out-patients, and the rest were private patients seen in the office.

The results of this year's work are summarized in tables 1 and 2. The former shows the number in each age group and the incidence of complications, the latter, the various types of complications present.

It is well known that in children and adolescents the treatment of diabetes with diet and standard insulin abounds in difficulties. The attempt to keep the blood sugar within normal limits necessitates a great deal of adjustment of amount of insulin and time of administration to prevent hypoglycemic reactions.

* Read at the St. Louis meeting of the American College of Physicians, April 22, 1937.

TABLE I
One Hundred Diabetic Patients to Whom Crystalline Insulin Was Given

Age Group	With Complications	Without Complications	Total
1-20	2	8	10
21-40	5	14	19
41-60	39	7	46
61 and over	15	10	25
Totals	61	39	100

TABLE II
Types of Complications Present in Diabetic Patients in This Study

Infections	Respiratory Lues Tuberculosis Osteomyelitis Carbuncle Ulcers of legs Acute iritis
Cardiovascular	Hypertension Cerebral hemorrhage Hemiplegias Coronary thrombosis Heart disease Hypertensive Arteriosclerotic Rheumatic Gangrene
Gastrointestinal	Peptic ulcer
Neurological	Neuritis Epilepsy Parkinson's disease
Ophthalmological	Cataracts Neuroretinitis with blindness
Other complications	Pregnancy Acidosis Uremia Pre-operative and post-operative

The 10 patients in our youngest group, those under 20 years of age, were successfully treated with crystalline insulin. Two were controlled with one dose daily, eight were controlled with two doses administered from 10 to 12 hours apart, the morning dose given one-half to one hour before breakfast and the evening dose either before or after the evening meal according to the individual indications. Seven of these children were attending school, and elimination of the noon dose of insulin—and in one case of a midnight dose also—was greatly appreciated. In this group two of the patients presented complications. A boy of seven had an active childhood tuberculosis with a daily rise in temperature. A girl of 19 had an infection of

the right index finger with osteomyelitis of the distal phalanx, due to a needle prick

The second group, 21 to 40 years of age, included wage-earners and housewives. All of the patients in this group were given crystalline insulin in two doses, at 10 to 14 hour intervals. The advantage of being able to go without a noon dose is very obvious in the cases of persons working in factories or offices. One of the young women in this group has pulmonary tuberculosis and she had found it a great hardship to have her sleep interrupted nightly for a 1 a m dose of insulin. With crystalline insulin, however, she has been able to keep her diabetes under control with two doses given 14 hours apart—at 8 a m and 10 p m.

The age group from 41 to 60 years included a good many patients manifesting various types of arteriosclerotic complications—coronary heart disease, hemiplegias, ophthalmoplegia, blindness due to vascular changes, hypertension and gangrene. There were also some other types of complications—cataracts, lues, tuberculosis and acute iritis. Arteriosclerotic manifestations were also present in the group from 61 to 86 years of age.

In the care of elderly diabetic patients with cardiovascular complications, it is especially important to prevent hypoglycemic reactions. Rapid reduction of the blood sugar level in this type of patient has been the cause of cerebral thrombosis, coronary thrombosis, visual disturbance due to thrombosis in the vessels of the fundi, and thrombosis in the peripheral vessels of the extremities. It would be difficult to estimate the mortality rate for the unskillful use of insulin. For this reason, in making clinical studies of insulins, it is just as important to judge the control of the diabetes from the standpoint of hypoglycemia as from that of hyperglycemia and glycosuria.

We have used crystalline insulin successfully pre-operatively and post-operatively in two cases, and also in the cases of three patients with acidosis. In these conditions, where glucose was administered every four hours either by mouth or intravenously, crystalline insulin was given every eight hours and the doses were determined by urine and blood examinations.

Crystalline insulin is administered subcutaneously in one or two doses. The morning dose is given one-half to one hour before breakfast and the second dose—if such is necessary—is given 10 to 14 hours later, either before or after the night meal depending upon the circumstances of the patient's eating arrangements. In a patient whose insulin requirement is unknown, we start with an arbitrary amount, 10-0-10, and adjust the dose according to the urine and blood examinations. If the patient had previously been on standard insulin, he is started on two-thirds of that amount of crystalline insulin divided into two doses.

In the entire group of patients to whom crystalline insulin has been given it has been noted that when there is an insulin reaction it comes about gradually unassociated with any shock. An opportunity afforded itself to note comparative shock effects of standard and of crystalline insulin in a

study of the use of insulin in the treatment of schizophrenia by our psychiatric department. Four non-diabetic schizophrenic patients were given insulin to produce shock. Sixty to 80 units of standard insulin produced a severe shock in all four patients, but 100 units of crystalline insulin did not cause any shock to three of the patients, and resulted, in the case of the fourth patient, in a light coma which was very readily relieved. Another observation was that with crystalline insulin it was possible to produce much lower blood sugar levels without resulting coma than was possible with standard.

Among the patients to whom crystalline insulin was administered no local reactions were observed. Ordinarily such reactions, which are considered allergic, may be expected in about 5 to 10 per cent of diabetic patients treated with insulin. It has been reported that crystalline insulin Abel¹⁰ and crystalline insulin Scott¹¹ have caused allergic reactions in certain sensitive individuals but much less so than noted with the standard commercial preparations. Perhaps after we have used crystalline insulin in a larger number of cases, we may also encounter allergic reactions. Crystalline insulin is a protein and therefore might cause reactions, but being a purer pancreatic extract, it is less likely to contain other pancreatic proteins than is standard insulin.

The condition of lipodystrophy which is noted occasionally at the site of insulin injection was present in three of our patients, and was very marked in two, producing deformed looking arms and thighs. The use of crystalline insulin over a period of 18 months has not produced this subcutaneous atrophy of the tissues in these patients.

From a year's experience with crystalline insulin, we have concluded that it can be used in any type of diabetes requiring insulin, with or without complications, except in diabetic coma with which condition we have not had any experience. Crystalline insulin is remarkably stable. We observed no clinical evidence of deterioration in a solution kept at room temperature for as long as a year.

Since Abel first crystallized insulin, studies have been made of its physiological, physical and chemical properties. Some of the findings offer a possible explanation for the greater efficiency of crystalline than of standard insulin. Observations have been recorded of a preliminary hyperglycemia following the injection of standard insulin, which led to investigations to determine whether this hyperglycemic action is a property of insulin or whether there is a secondary accompanying substance in the insulin. Burger and Kramer,¹²⁻²¹ who have made a large number of chemical and physical comparative studies, believe that they have been able to isolate a hyperglycemic principle from standard insulin which they call Glukagon. Their studies show that this principle is not present in crystalline insulin. Geiling and DeLawder²² investigated this point and concluded that the hyperglycemic action was due solely to impurity and that crystalline insulin did not

produce any preliminary hyperglycemia because of the absence of this impurity. Tangl and Than²⁹ confirmed the presence of such impurities in standard insulin by isolating a pancreatic extract possessing marked hyperglycemic properties.

Thus, evidence points to the presence of a substance in standard insulin, whether it be a separate hormone or an impurity, which causes hyperglycemia, and so obviously must decrease the efficiency of the insulin. This substance is not present in crystalline insulin. This seems a logical explanation of the greater efficiency of crystalline insulin than of standard

SUMMARY

Crystalline insulin has been used in the treatment of diabetes in 100 patients ranging in age from 6 to 86 years. Sixty-one of these patients had various types of complications, 39 were without complications. In some of these patients the diabetes was well controlled with one dose of crystalline insulin. None of them required more than two doses which were administered 10 to 14 hours apart.

Insulin reactions were rare, and when they did occur were not associated with as much shock as is experienced with standard insulin, much lower blood sugar levels were obtained without manifest symptoms of reaction. No local reactions were observed in this entire group. The condition of lipodystrophy, which was present in three patients following the use of standard insulin, was not observed when crystalline insulin had been in constant use for 18 months.

Possible explanations for the increased efficiency of crystalline insulin are presented.

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ELECTROCARDIOGRAPHIC CHANGES FOLLOWING EXTERNAL CHEST INJURY TO DOGS^{*}

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MEDICAL literature contains considerable evidence, obtained by autopsy, that non-penetrating wounds to the chest can produce severe traumatic lesions in the pericardium, heart and great vessels, but it is not generally accepted that less severe trauma can cause mild changes in the heart which have a tendency to recover

Beck¹ described experiments on dogs where the heart was exposed and contused. The resultant myocardial injuries produced electrocardiographic changes similar to those obtained in coronary artery occlusion, affecting chiefly the Q- and T-wave and having a tendency to return to normal. Randles, Gorham and Dresbach² described alternation in the RS-T component of the electrocardiogram simulating those associated with coronary artery occlusion, produced in dogs by experimental auricular rupture and the resulting hemopericardium. It was their opinion that the variation of the RS-T component was due to the amount of fluid in the pericardial sac and not the auricular injury.

In order to ascertain whether electrocardiographic changes do occur following external chest injury, and if so, the type of changes, the speed with which they occur, the amount of required trauma and the lesions produced, a series of experiments was performed on dogs in which electrocardiographic and pathological studies were made following varying degrees of injury to the chest but not to the heart direct.

• PROTOCOLS

Dog 1 (figure 1) A young mongrel dog, weight 30 pounds, was given 1 gm of sodium amytal intraperitoneally and one hour later the control electrocardiogram *A* was taken. A $\frac{3}{4}$ inch board was placed over the sternum and one heavy blow was struck with a hard rubber mallet and electrocardiogram *B* was taken in five minutes. Ten minutes after the first blow, a second similar blow was struck in the same manner. This was followed by a jerky type of respiration using chiefly the external thoracic muscles. Electrocardiogram *C* was taken 10 minutes after, *D*, 20 minutes after, *E*, one and one-half hours after, *F*, two and one-half hours after, and *G*, five and one-half hours after the second blow. At this time the dog was killed by chloroform and an autopsy performed which revealed hemorrhage into the anterior and posterior mediastinal spaces and about the roots of both lungs. The microscopic examination revealed hemorrhagic infiltration of the lungs, a small hemorrhage beneath the endocardium at the base of the mitral valve and a small hemorrhage beneath the endocardium of one of the cusps of the pulmonary valve.

^{*} Presented at the St. Louis meeting of the American College of Physicians, April 23, 1937.

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Dog 2 (figure 2) A mongrel bitch, weight 35 pounds, was given 1 gm of sodium amytal intraperitoneally and one hour later the control electrocardiogram *A* was taken. A $\frac{3}{4}$ inch board was placed over the upper sternum and two moderately heavy blows were struck with a hard rubber mallet and electrocardiogram *B* was

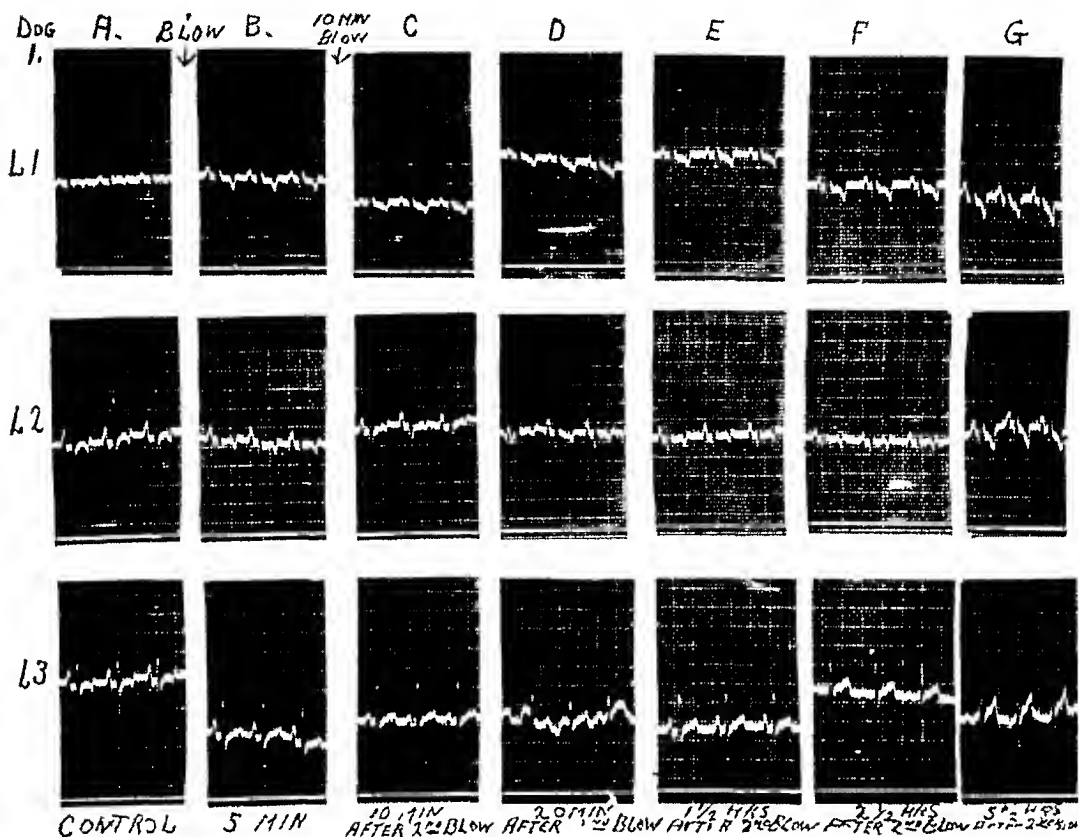


FIG 1 Dog 1

taken in 10 minutes, *C* in one hour, *D* in three hours and *E* in five hours. At this time another similar blow was struck and electrocardiograms *F*, *G* and *H* were taken 10 minutes, one-half hour and three-quarters hour later. At this time the animal was killed by chloroform and an autopsy performed which revealed no abnormal lesions of the heart but moderate atelectasis, congestion and a slight amount of hemorrhage of both lungs.

Dog 3 (figure 3) A young mongrel dog, weight 30 pounds, was given 1 gm of sodium amytal intraperitoneally and one hour later the control electrocardiogram *A* was taken, the sternum was now struck a heavy blow with an ordinary hammer and electrocardiograms *B*, *C* and *D* were taken five minutes, one-half hour and three-quarters hour later. At this time a second similar blow was struck and electrocardiograms *E* and *F* were taken in five minutes and in one hour. A third series of two similar blows was now struck and following these electrocardiograms *G* was taken in one-half hour and *H* in one hour. The animal was now killed by chloroform and an autopsy performed which revealed moderate hemorrhage and atelectasis about the right lung root.

Dog 4 (figure 4) A mongrel dog, weight 25 pounds, was given 0.75 gm of sodium amytal intraperitoneally and one hour later the control electrocardiogram *A*

was taken. A $\frac{3}{4}$ inch board was placed over the sternum and a heavy blow was struck with a 10 pound sledge hammer and electrocardiograms *B*, *C*, *D* and *E* were taken five minutes, one-half hour, one and one-half hours and two and one-half hours later. The animal was killed by chloroform and an autopsy performed that revealed small subendocardial hemorrhages into the right and left posterior cusps of the aortic valve.

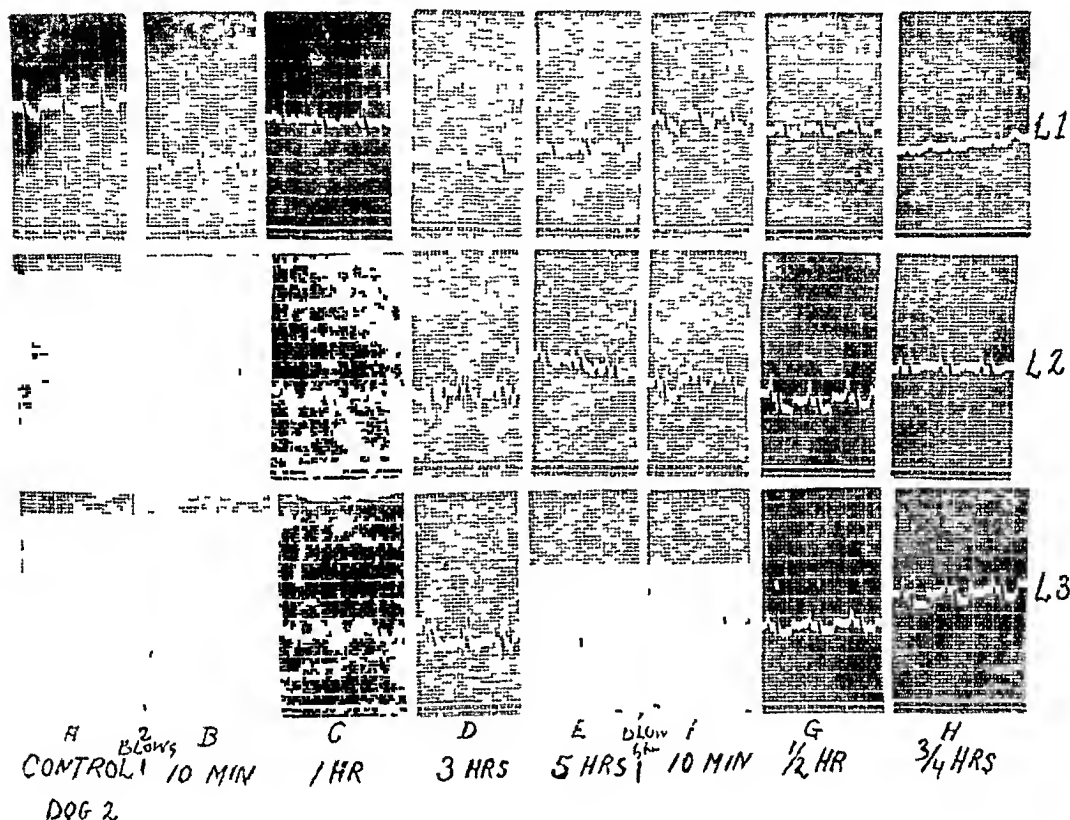


FIG 2 Dog 2

Dog 5 (figure 5) A young mongrel bitch, weight 24 pounds, was given 1 gm of sodium amytal intraperitoneally and one hour and 15 minutes later the control electrocardiogram *A* was taken. A $\frac{3}{4}$ inch board was placed on the left chest over the point of maximal intensity of the apex beat and one full blow delivered with a 10 pound sledge hammer while the electrocardiogram was attached in Lead II with the camera running. The string was protected for only a second while the blow was struck, and immediately afterwards brought back into the camera field and standardized, revealing by the timer that electrocardiogram *B* was taken twelve seconds after the blow was struck (figure 6). Electrocardiogram *C* was taken in five minutes, *D* in one-half hour, *E* in one hour, and *F* in one and one-half hours after the blow was struck. Five minutes after the last electrocardiogram was taken a second blow was delivered in the same manner and the electrocardiogram *G* (figure 7) was taken within a few seconds. Electrocardiogram *H* (figure 8) was taken in 10 minutes, *I* in one and one-quarter hours, *J* in one and one-half hours, and *K* in two and one-half hours after the second blow. At this time the dog was killed by chloroform and an autopsy performed which revealed the peritoneal cavity filled with recent hemorrhage.

originating from two tears in the liver, one in the dome of the right lobe which was 3 cm long, 1 cm wide and 2 cm deep, and another upward from the gall-bladder 3 cm and extending through the entire thickness of the liver at this point. There was no free hemorrhage in the pericardial sac but hemorrhage into the parietal wall of the pericardium anteriorly and into the tissues about the base of the heart. The microscopic examination did not reveal any abnormal lesions.

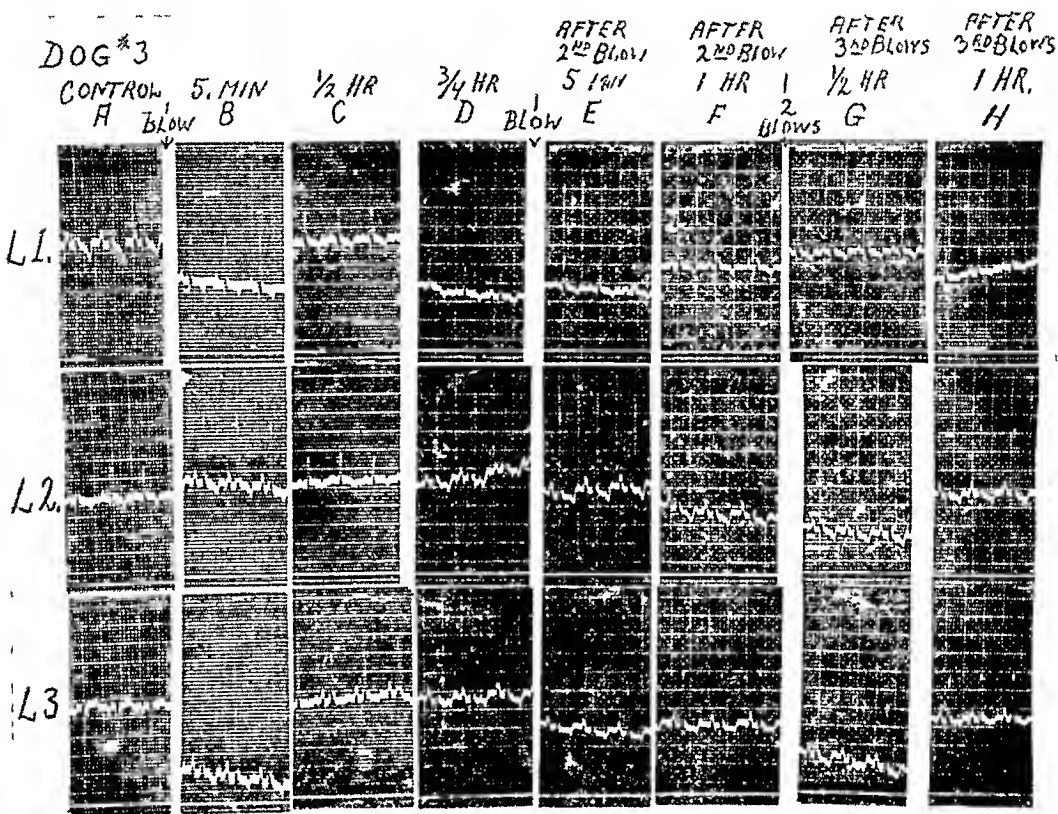


FIG 3 Dog 3

Dog 6 (figure 9) A mongrel dog, weight 60 pounds, was given 15 gm of sodium amytal intraperitoneally and one and one-half hours later the control electrocardiogram *A* was taken. A $\frac{1}{4}$ inch board was placed over the left chest of the dog and one hard blow was struck with a four pound hammer, and one minute later electrocardiogram *B* was taken. Fifteen minutes after the first blow electrocardiogram *C* was taken and a minute later another blow was struck in the same manner, then one minute after the second blow electrocardiogram *D* was taken. Fifteen minutes after the second blow electrocardiogram *E* was taken, and one minute later two blows were delivered in the manner described and electrocardiogram *F* was taken one minute after the third series of blows. After a 15 minute period electrocardiogram *G* was taken and again, one minute later, two more blows were delivered in the manner described and the electrocardiogram *H* was taken in one minute, and *I* in 15 minutes after this fourth series of blows. At this time the dog, still under anesthesia, was taken to a veterinary hospital where he shortly regained consciousness but was found dead in his cage 10 hours later. At autopsy there was found a clean-cut one inch tear in the anterior parietal pericardium, with a moderate amount of free

hemorrhage in the pericardial sac, and a four inch rent in the posterior part of the right diaphragm. There was a contusion with a marked degree of hemorrhage of the entire right lung and of the base of the left lung. Shortly before the dog died the respiration was very rapid and shallow, temperature 106° , heart sounds normal, but many moist rales were heard throughout the chest. Microscopic examination revealed moderate atelectasis and hemorrhagic infiltration of the lungs.

DOG #4

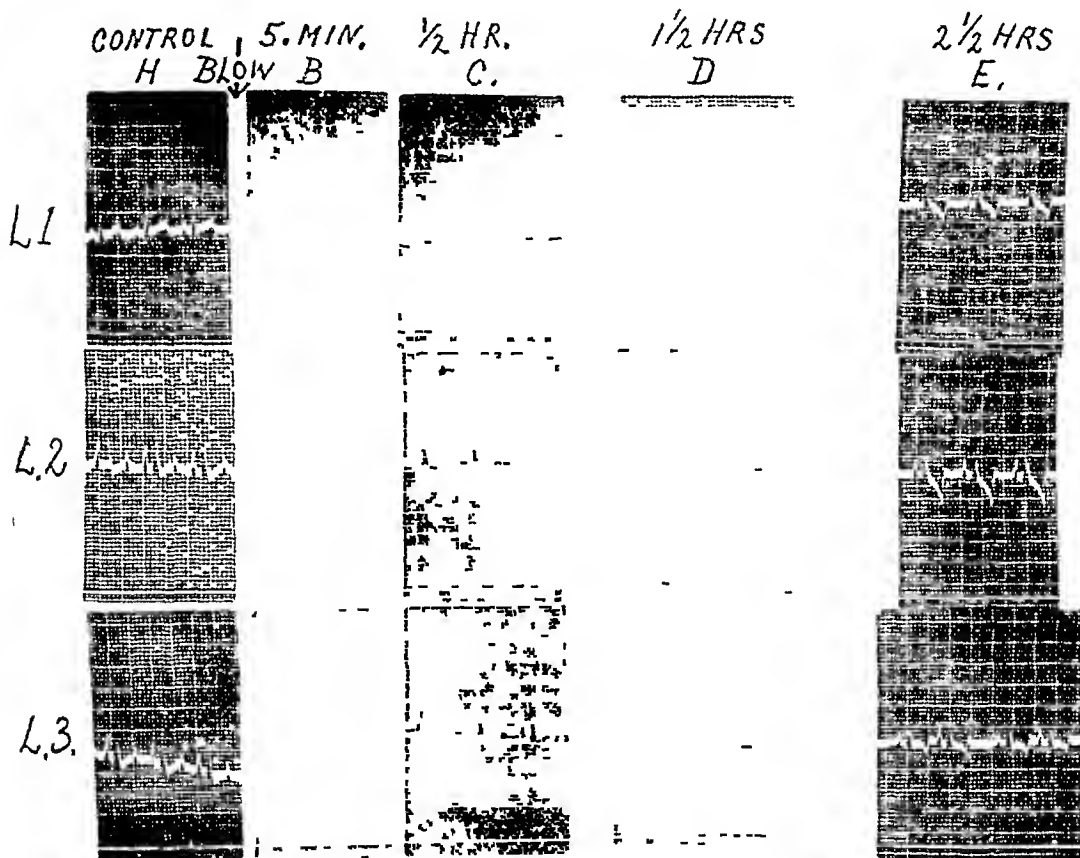


FIG 4 Dog 4

Dog 7 (figure 10) A hound dog, weight 35 pounds, was given 0.75 gm of sodium amytal intraperitoneally and one hour later the control electrocardiogram A was taken. One hard blow was struck with a five pound hammer to the point of maximal cardiac pulsation on the left chest, and after 25 minutes electrocardiogram B was taken, and after two hours electrocardiogram C was taken. The dog was now taken to a veterinary hospital. There was no increase in the respirations nor any elevation of temperature, and the heart sounds appeared normal. The next day the dog was up and about, and appeared normal. There were no signs of tenderness on the chest wall. On the sixth day electrocardiogram D was taken and on the seventh day the dog coughed and spit blood, passed blood in the stool and had five attacks of syncope. On the eighth day electrocardiogram E was taken, and on the twenty-first day electrocardiogram F was taken. At this time the veterinarian reported that following exercise the dog would have an irregular heart rhythm.

DOG #5.

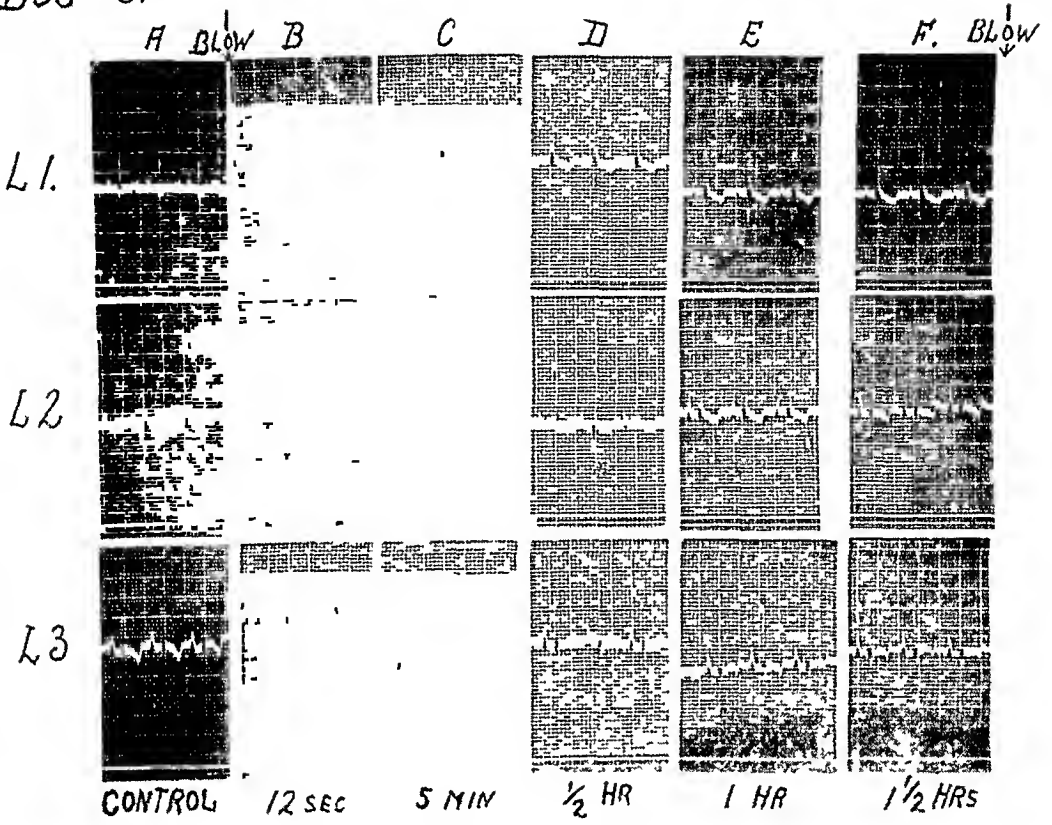


FIG 5 Dog 5

DOG #5

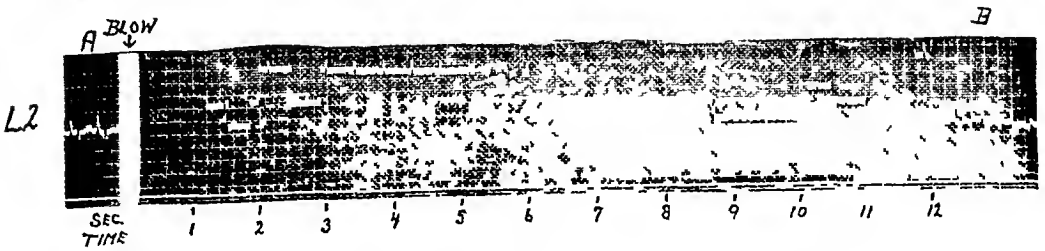


FIG 6 Dog 5 A (control) is the same as A in figure 5 B, 12 seconds after blow, same as B in figure 5

Electrocardiogram *G* was taken on the fortieth day and *H* on the one hundredth day after the blow was delivered, and on the one hundred and twenty-first day the dog suddenly dropped dead. An autopsy revealed no gross abnormal lesions except that the anterior parietal pericardium was slightly thickened. A microscopic examination revealed partial atelectasis, slight congestion and moderate hematogenous pigmentation of the lungs. The left coronary artery showed moderate subintimal and medial thickening with a vacuolization and loss of elastic tissue fibers.

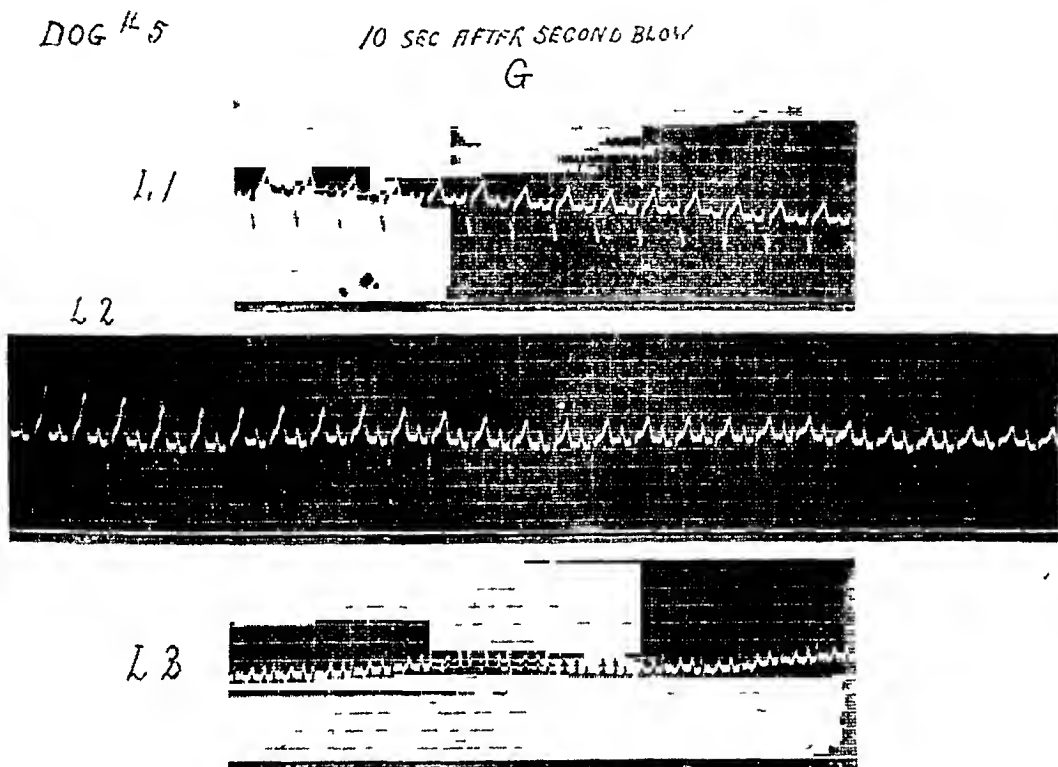


FIG 7 Dog 5 Lead II taken first, Lead I second and Lead III last

Dog 8 (figure 11) A short haired mongrel bitch, weight 22 pounds, was given 0.50 gm of sodium amytal intraperitoneally and one hour later the control electrocardiogram *A* was taken. Following this two hard blows were struck with a five pound hammer on a $\frac{1}{4}$ board placed over the area of maximum intensity of the apex beat on the left chest, and one minute later electrocardiogram *B* was taken. At this time respiration ceased for a short period and then started with an irregular rhythm. Twenty minutes after the blows were struck electrocardiogram *C* was taken, and 50 minutes after electrocardiogram *D*. The dog was then taken to the veterinary hospital. The next morning she was up and about, apparently normal. On the second day after the start of the experiment electrocardiogram *E* was taken, and on the third day the animal died during sleep. An autopsy revealed no injury to the anterior chest wall, though there was a small hole in the anterior pericardium with about 5 cc of blood in the pericardial sac. There was no hemorrhage in the anterior or posterior mediastinal spaces, and a microscopic examination did not reveal any abnormal lesions.

Dog 9 (figure 12) A hound bitch, weight 26 pounds, was given 0.75 gm of sodium amytal intraperitoneally and 45 minutes later the control electrocardiogram *A*

was taken, and following this two hard blows with a five pound hammer were struck on a $\frac{1}{4}$ inch board placed over the area of maximum intensity of the apex beat on the left chest. One minute after these blows electrocardiogram *B*, and 45 minutes after electrocardiogram *C* were taken. The animal was then taken to the veterinary hospital, and the next morning she was up and about, apparently normal. On the seventh day after the start of the experiment electrocardiogram *D* was taken, and on the sixteenth day the animal was found dead. An autopsy did not reveal any gross

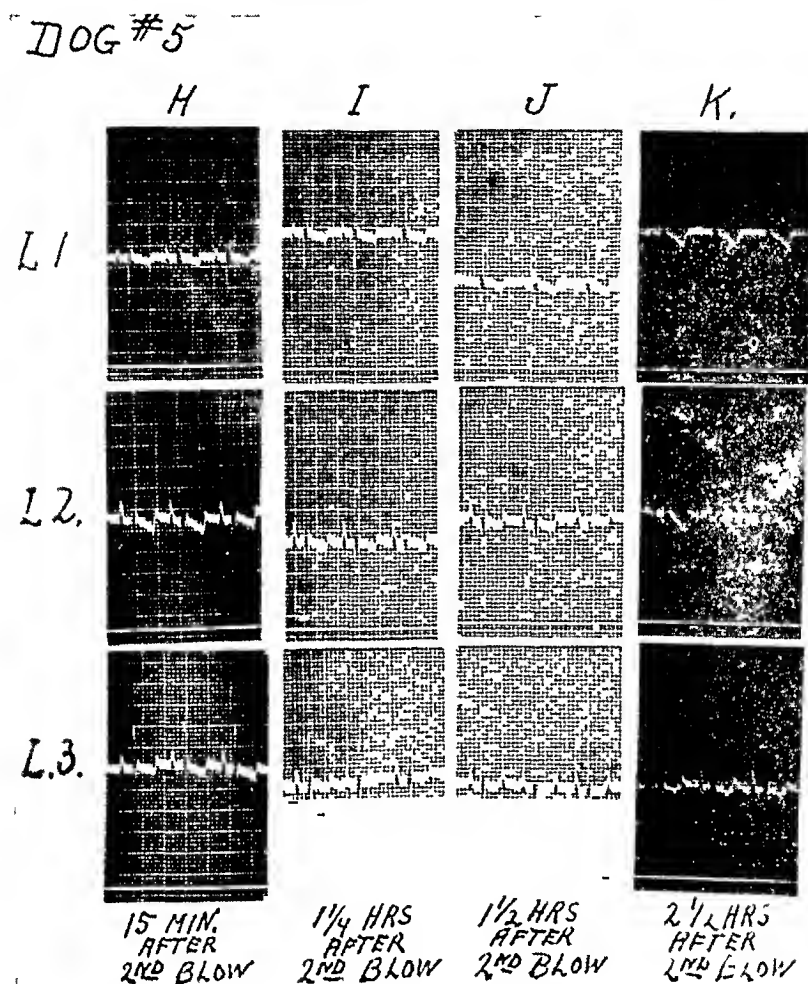


FIG 8 Dog 5

abnormal lesions, and a microscopic examination showed moderate congestion of the lungs and a moderate number of heart failure cells.

Dog 10 (figure 13) A German Shepherd bitch, weight 45 pounds, was given 15 gm of sodium amytal intraperitoneally, and one hour later the control electrocardiogram *A* was taken. Two hard blows with a five pound hammer were struck directly on the area of maximum intensity of the cardiac apex beat on the left chest and electrocardiogram *B* was taken in one minute, *C* in two minutes, *D* in three minutes, *E* in four minutes, *F* in five minutes, *G* in seven minutes (figure 14), *H* in eight minutes, *I* in 12 minutes, *J* in 13 minutes, *K* in 14 minutes, *L* in 15 minutes, and *M* in 16 minutes following the blows. At this time the animal died and an autopsy

Dog 6

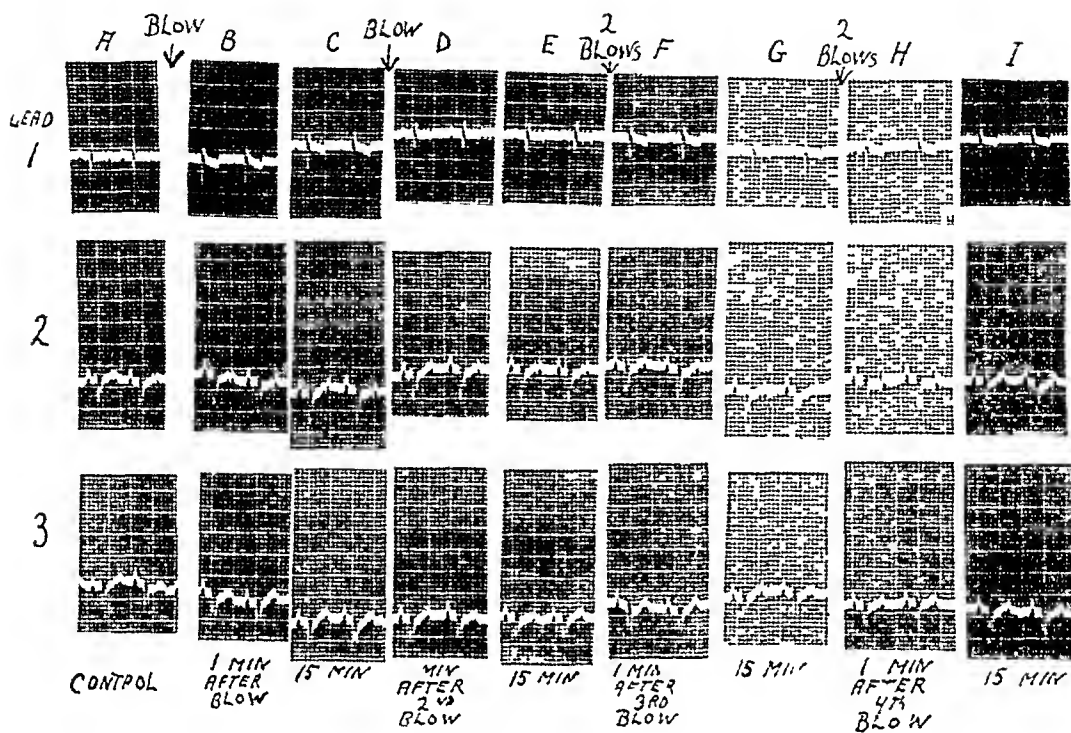


FIG 9 Dog 6

Dog #7

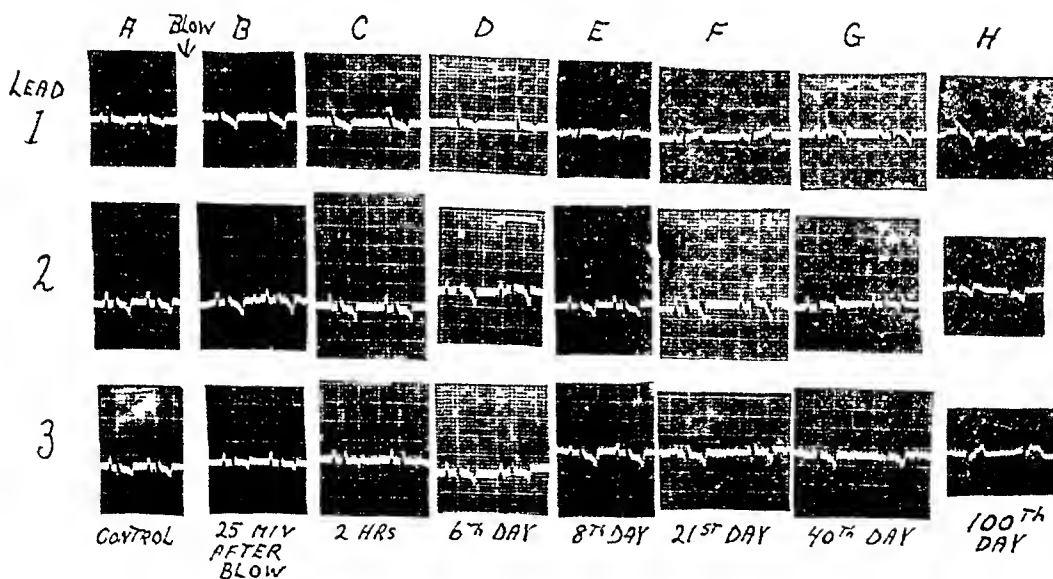


FIG 10 Dog 7

was performed. Gross and microscopic examinations did not reveal abnormal lesions.

Dog 11 (figure 15) A mongrel bitch, weight 17 pounds, was given 0.5 gm sodium amytal intraperitoneally, and one hour later control electrocardiogram *A* was taken. Immediately afterwards one hard blow was struck with a five pound hammer on the area of maximum intensity of the apex beat on the left chest wall. Following this blow electrocardiogram *B* was taken in two minutes, *C* in three minutes, *D* in four minutes, *E* in six minutes (figure 16), *F* in eight minutes, *G* in 11 minutes, *H* in 14 minutes, and *I* in 21 minutes (figure 17), at which time the animal died. An autopsy was performed, but gross and microscopic examinations failed to reveal any abnormal lesions.

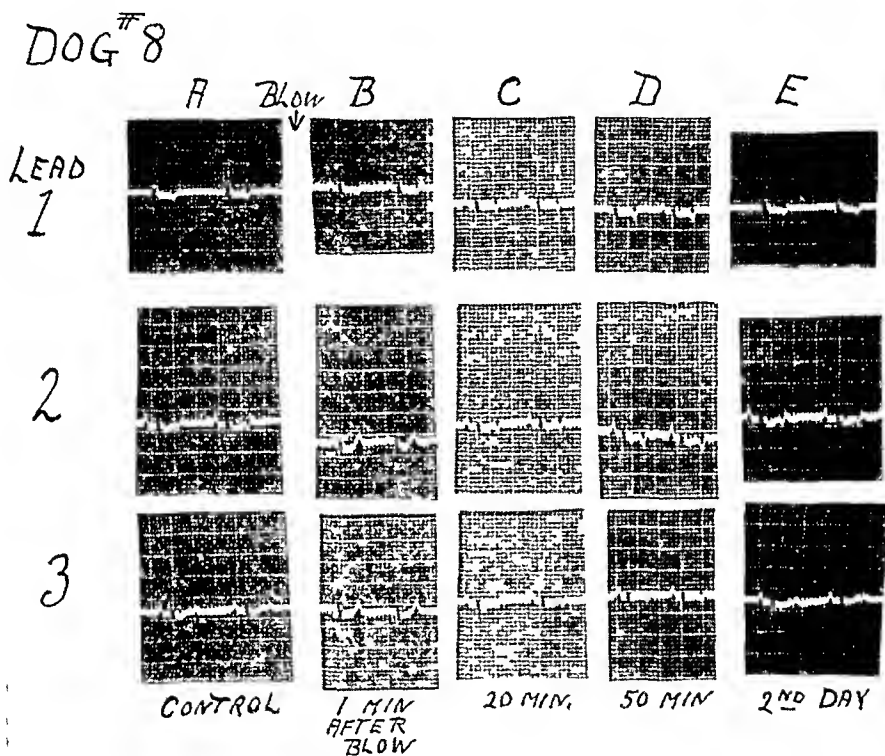


FIG 11 Dog 8

Dog 12 (figure 18) A short-haired mongrel bitch, weight 15 pounds, was given 0.5 gm of sodium amytal intraperitoneally and one hour later the control electrocardiogram *A* was taken. One heavy blow with a 10 pound hammer was delivered to the left chest of the animal, and one minute later electrocardiogram *B* was taken, and four minutes later electrocardiogram *C* was taken. At this time another blow of the same type was struck (figure 19), and in one minute electrocardiogram *D* and in nine minutes electrocardiogram *E* were taken. A similar blow was again delivered, and following this electrocardiogram *F* was taken in one minute, *G* in three minutes, and (figure 20) *H* in 13 minutes. Again a similar blow was delivered and following this electrocardiogram *I* was taken in one minute and *J* in four minutes at which time the animal died. An autopsy was performed which revealed free blood in both pleural cavities, hemorrhage in the anterior and posterior mediastinal spaces, contusion of the entire right lung with a small marginal rupture of both this and the left

lung There was hemorrhage about the base of the heart and a three inch rupture in the parietal pericardium anteriorly where it joins the great vessels, with a small amount of free hemorrhage in the pericardial sac There was an area of contusion one inch in diameter, with hemorrhage in the anterior wall of the right auricle close to the superior vena cava Microscopic examination revealed slight hemorrhage beneath the visceral pericardium of the right auricular myocardium and moderate hemorrhage of the lungs

Dog 13 (figure 21) A short-haired mongrel dog, weight 25 pounds, was given 0.75 gm sodium amytal intraperitoneally, and one hour later the control electro-

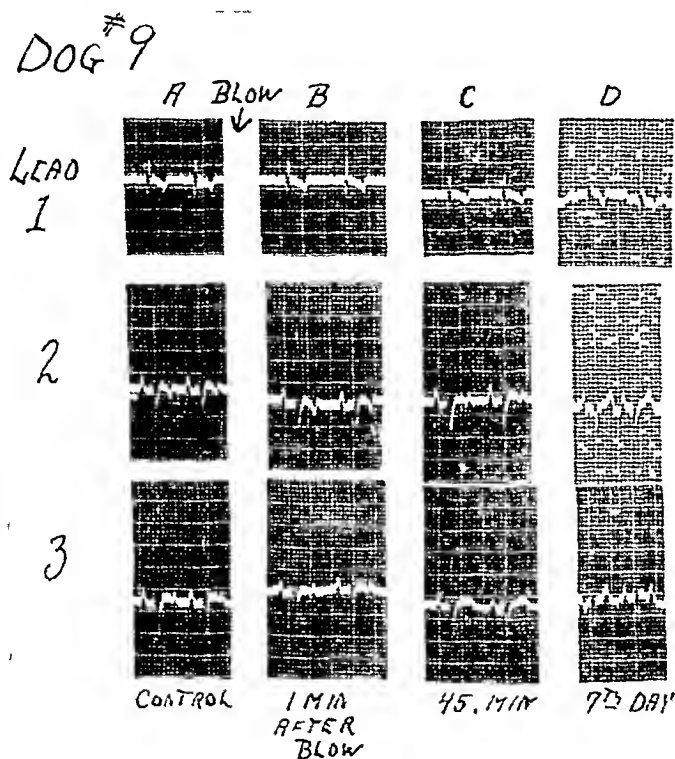


FIG 12 Dog 9

cardiogram *A* was taken Then while electrocardiogram *B* was being taken one hard blow was struck with a 10 pound hammer to the left chest of the animal Following this (figure 22) electrocardiogram *C* was taken in one minute, *D* in four minutes, *E* in five minutes, *F* in eight minutes, and *G* in 11 minutes at which time the dog died An autopsy was performed which revealed hemorrhage into the anterior and posterior mediastinal spaces, hemorrhage into the tissue about the great vessels, also small areas of contusion and hemorrhage into the myocardium of the anterior wall of the right and left auricles There was a small amount of free blood in the pericardial sac Microscopic examination revealed a small amount of hemorrhage under the visceral pericardium of the right and left auricular myocardium

Dog 14 (figure 23) A German Shepherd dog, weight 70 pounds, was given 1.5 gm of sodium amytal intraperitoneally, and one hour later control electrocardiogram *A* was taken, following which the right and left vagus nerves and the superior and middle cervical ganglions were cut on both sides, and the spinal cord severed between the third and fourth cervical vertebrae, and after this was accomplished the

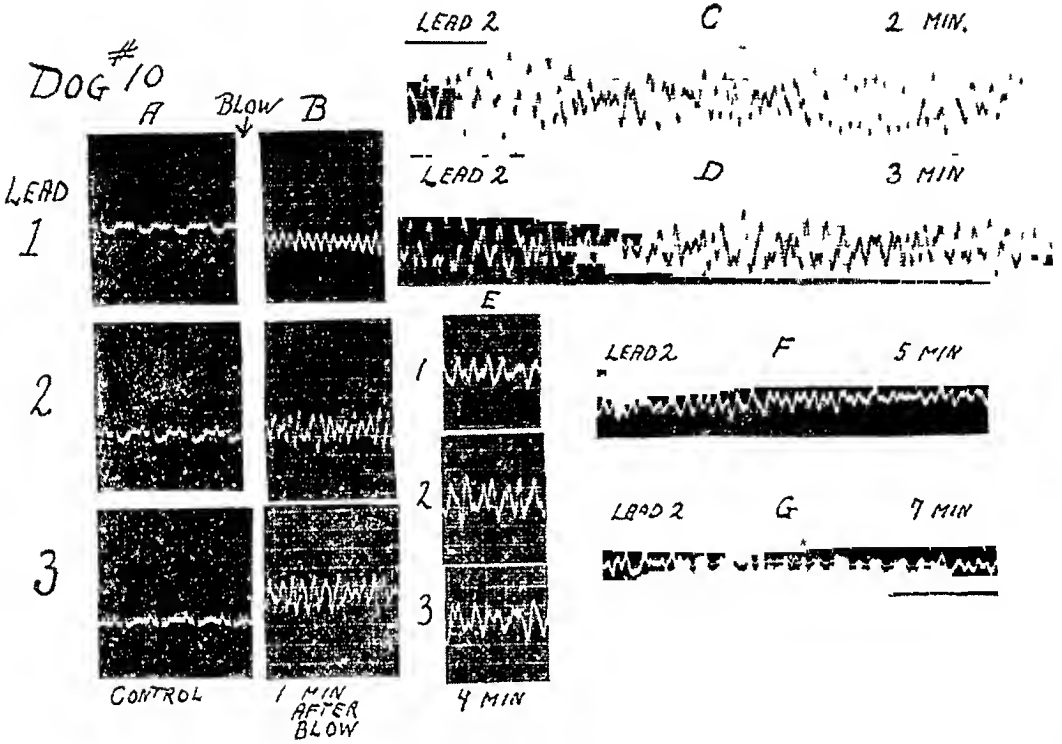


FIG 13 Dog 10

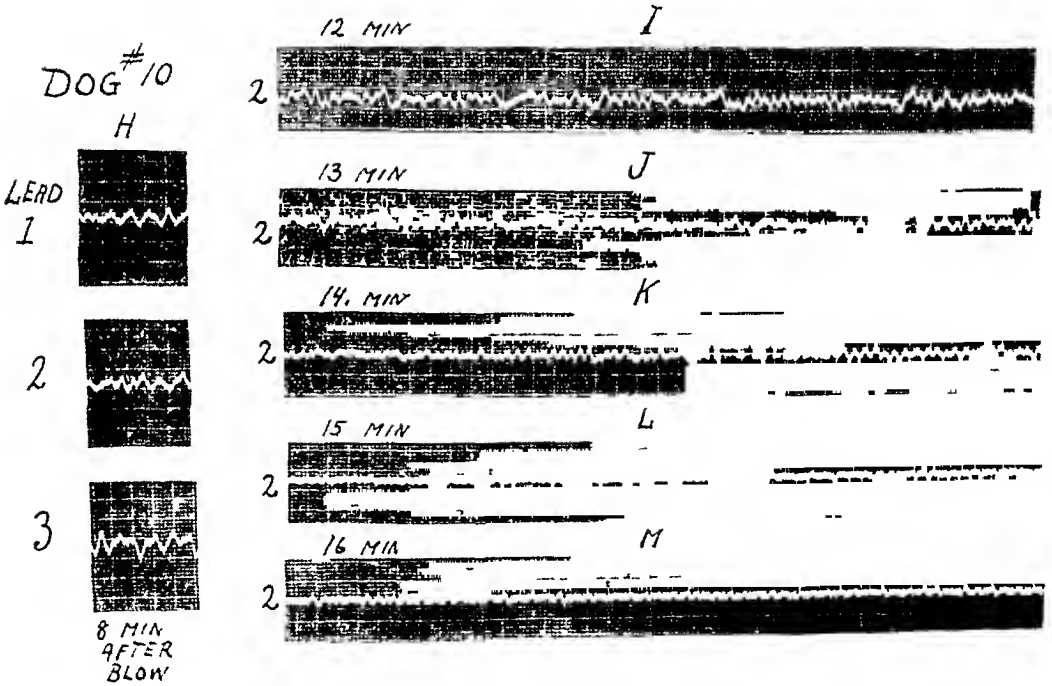


FIG 14 Dog 10

control electrocardiogram *B* was taken While electrocardiogram *C* was being taken a hard blow was struck with a five pound hammer directly to the left chest at the point of maximum intensity of the apex beat Five minutes later while electrocardiogram *D* was being taken the same type of blow was again delivered, and the same procedure repeated in five more minutes while electrocardiogram *D* was being

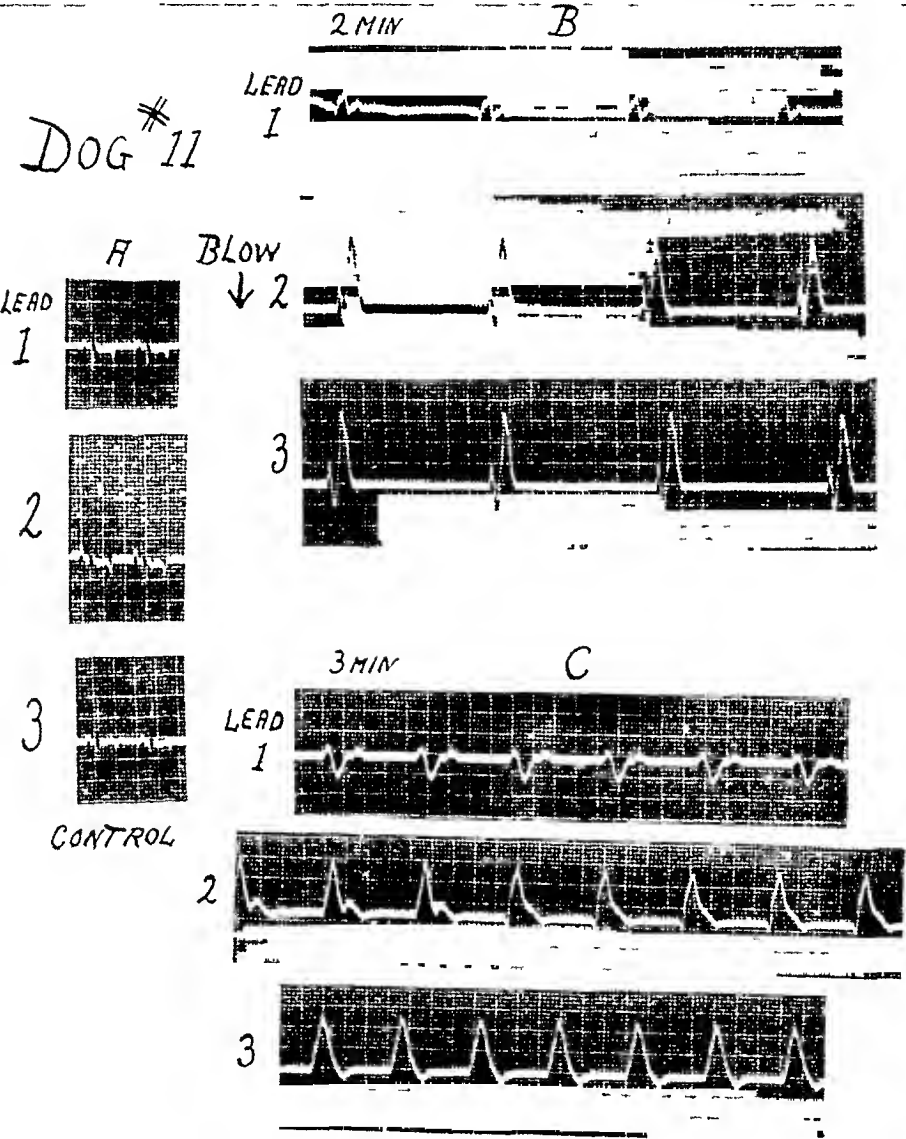


FIG 15 Dog 11

taken Thirty-one seconds after electrocardiogram *D* the electrocardiogram *F* (figure 24) was taken, and five minutes after the previous blow another similar one was delivered while electrocardiogram *G* was being taken followed in one minute by electrocardiogram *H* Five minutes after the previous blow another similar blow was delivered while electrocardiogram *I* was being taken Five minutes later this procedure was repeated while electrocardiogram *J* (figure 25) was being taken

Three seconds later electrocardiogram *K* was taken, two minutes *L*, four minutes *M*, and six minutes later electrocardiogram *N*. Five minutes after this last electrocardiogram another similar blow was struck while the electrocardiogram *O* (figure 26) was being taken, and one minute later electrocardiogram *P* was taken. After a five minute interval another similar blow was struck while electrocardiogram *Q* was being taken and the tracings *R* and *S* (figure 27) are continuous with the previous electrocardiogram. *T* was taken three seconds later and *U* 42 seconds after this. Five minutes after this last electrocardiogram another blow of the same type

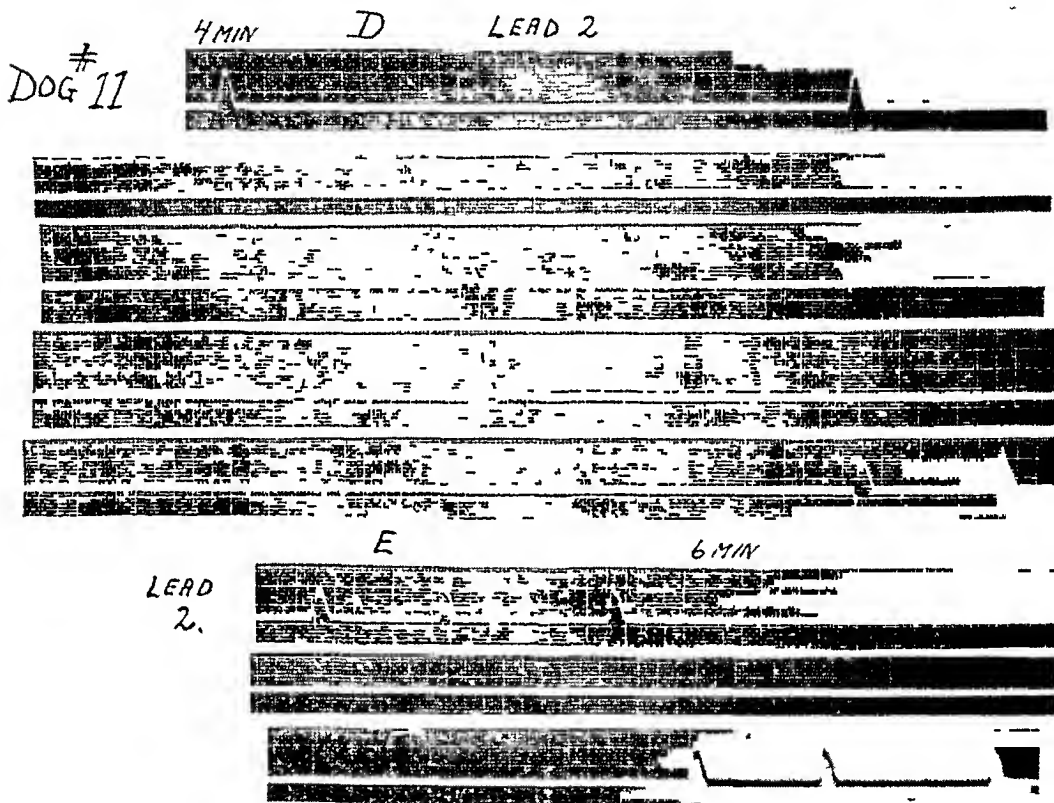
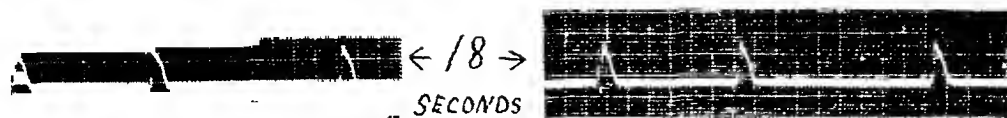


FIG 16 Dog 11

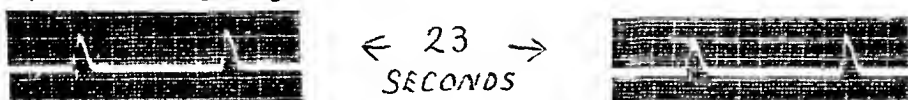
was delivered while electrocardiogram *V* was being taken, and the procedure repeated in five more minutes while electrocardiogram *X* (figure 28) was being taken. Electrocardiogram *W* was continuous, and then again the blow was repeated, while electrocardiogram *Y* was being taken. At this time the dog was killed by chloroform and an autopsy performed which showed that the right and left vagus nerves had been cut, as well as the superior and middle cervical ganglions on both sides and the spinal cord. There was a small amount of ecchymosis into the intercostal muscles of the third and fourth left interspaces just to the left of the sternal margin, and the second and third ribs on the right were fractured without displacement at the costochondral junction. Corresponding to these external injuries were small areas of ecchymosis in the pleura. There was a moderate amount of hemorrhage in the extreme apical portion of both lungs. The pericardial sac contained about two ounces of clear fluid and on the anterior visceral pericardium near the apex was a small roughened opaque area two cm in diameter, while just to the left of this was a

DOG #11

F 8 MIN LEAD 2



G 11 MIN LEAD 2



H 14 MIN LEAD 2

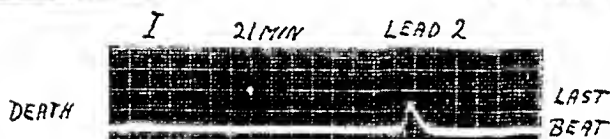
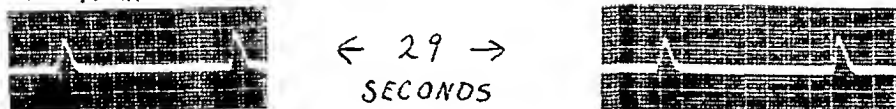


FIG 17 Dog 11

DOG #12

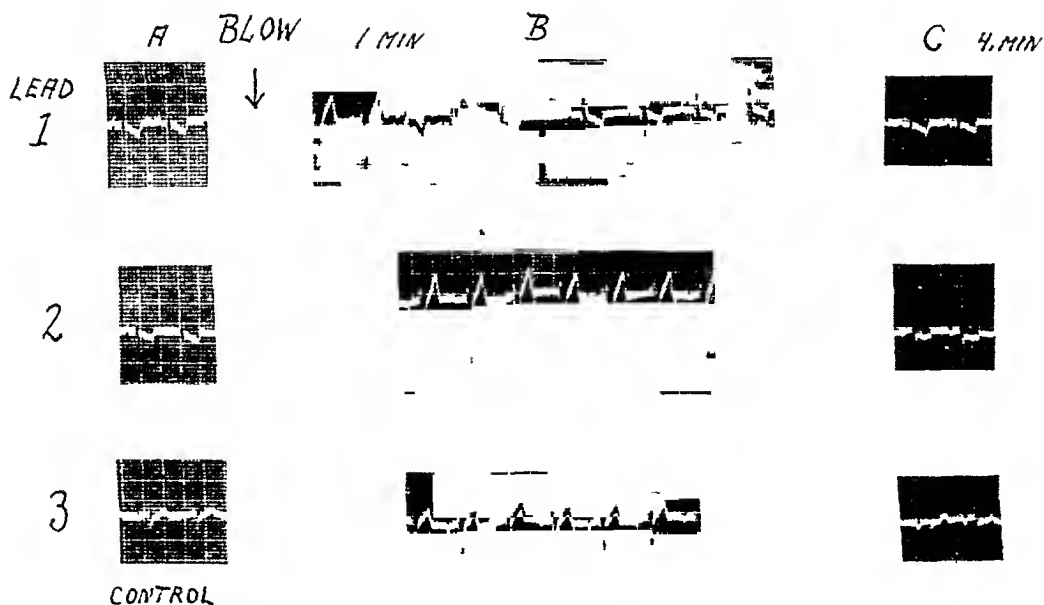


FIG 18 Dog 12

small area of hemorrhage and muscle contusion. There was a small rupture 6 mm in length between the anterior cusp and the right posterior cusp of the aortic valve with moderate hemorrhagic infiltration about the base of this valve but no invasion of the myocardium. Microscopic examination revealed the hemorrhages of the anterior wall and the septal portion of the left ventricle to be limited to the subendothelial tissue and not to invade the myocardium. Sections taken through the area of pericardial thickening on the anterior surface of the left ventricle revealed an old pericardial scar consisting of fibrous tissue which in some areas was piled up in a villus like manner. The lungs showed extensive hemorrhagic infiltration of the interstitial tissue and the alveoli and a moderate amount of atelectasis.

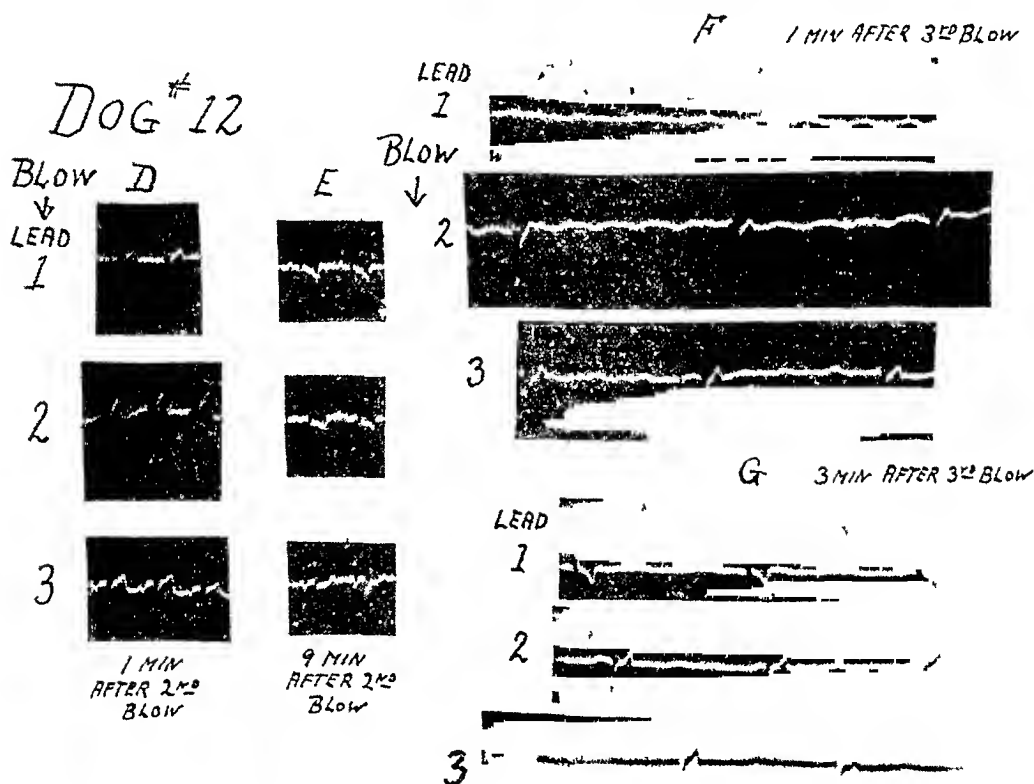


FIG 19 Dog 12

Dog 15 (figure 29) A mongrel English setter, weight 35 pounds, was given 0.75 gm of sodium amytal intraperitoneally, and one hour later the control electrocardiogram *A* was taken. At this time both vagus nerves, the superior and middle cervical ganglions on both sides, and the spinal cord between the third and fourth cervical vertebrae were cut. Following this control electrocardiogram *B* was taken, and then while electrocardiogram *C* was being taken a hard blow was struck with a five pound hammer to the area of maximum intensity of the apex beat on the left chest wall, one minute later electrocardiogram *D* was taken. Then five minutes after this electrocardiogram another similar blow was delivered while the electrocardiogram *E* was being taken, and one minute later electrocardiogram *F* was taken. After a five-minute interval another similar blow was struck while electrocardiogram *G*

(figure 30) was being taken, and again the procedure was repeated after a five-minute interval while electrocardiogram *H* was being taken and electrocardiogram *I* starts 62% seconds after *H*, and is continued on electrocardiogram *J* (figure 31). The electrocardiograms follow each other after various time intervals, *K* after 15% seconds, *L* one minute later, *M* (figure 32) 13% seconds later, *N* two minutes later, *O* three minutes later, *P* two minutes later, and *Q* two and one-half minutes later, at which time the dog died. An autopsy showed that the right and left vagus nerves

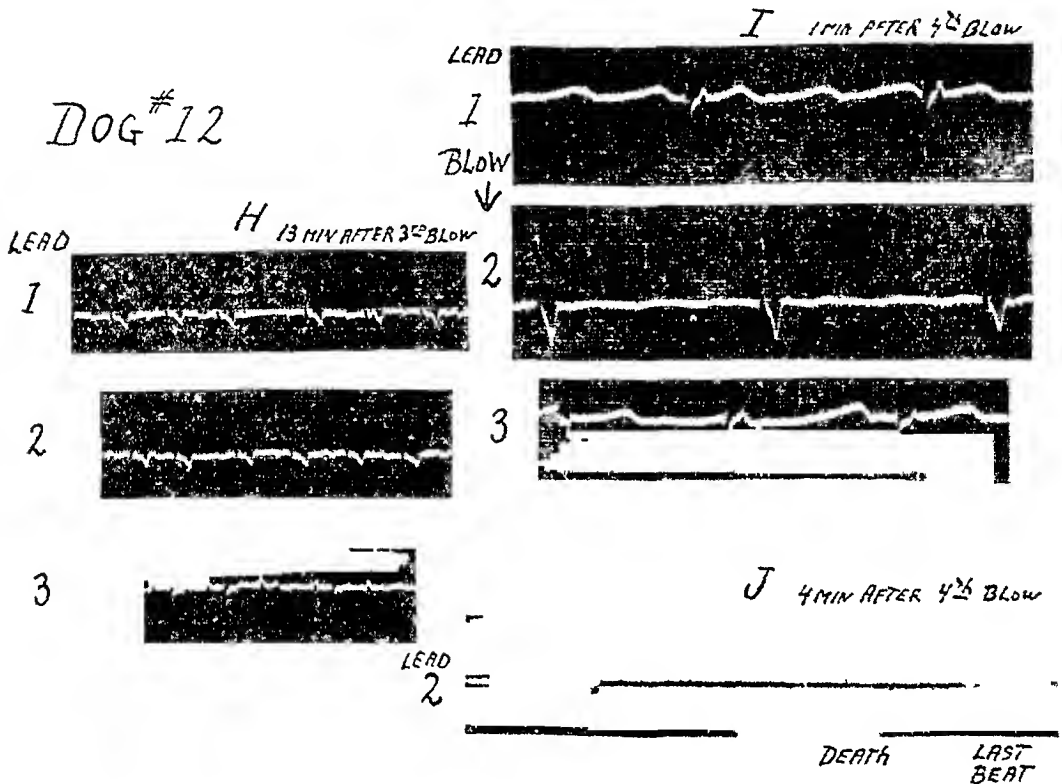


FIG 20 Dog 12

had been cut as well as the superior and middle cervical ganglions on both sides and the spinal cord. There was a small rent two inches long through the intercostal muscle of the left fourth intercostal space about two inches from the sternal margin with slight ecchymosis of the surrounding muscle tissue, but there were no fractures of the ribs or sternum. There was a massive collapse of both lungs with a small amount of bloody fluid into the pleural cavities. There were two tears about one cm in length in the endocardium of the auricles, one close to the superior vena cava and the other just above the mitral valve. There was also a small rent in the superior surface of the liver. Microscopic examination revealed some atelectasis and moderate hemorrhagic infiltration of the lungs. Sections of the tears in the auricles showed a superficial absence of the endocardium which was replaced by fresh hemorrhage infiltrated slightly into the underlying muscle tissue.

GENERAL REMARKS

All electrocardiograms were taken in Leads I, II and III unless otherwise stated, and all leads were standardized at the time of each electrocardiogram. The electrodes used were of the ordinary small metal type, and the position of the animal remained the same throughout each experiment, but

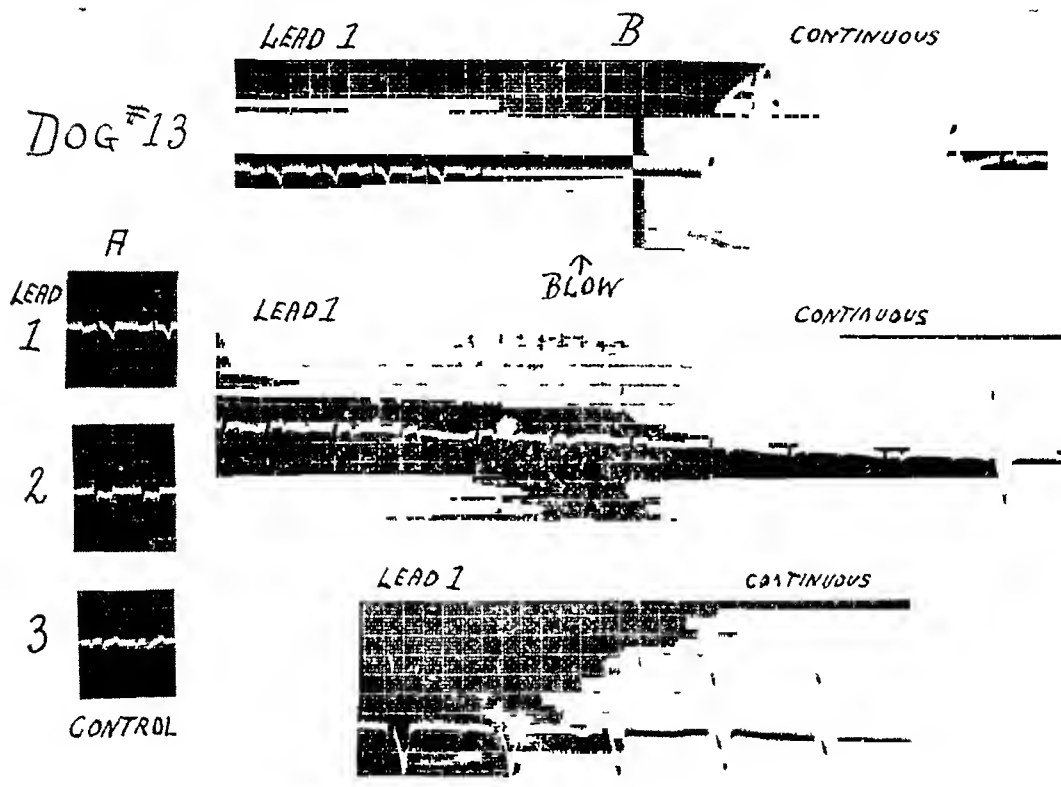


FIG 21 Dog 13

the animals that were allowed to recover from the anesthesia and live were taught to stand still while the electrocardiograms were taken. Many microscopic sections were studied on each animal from the pericardium, walls of the great vessels, myocardium, coronary vessels, cusps of the valves, conduction system and lungs.

ELECTROCARDIOGRAPHIC RESULTS

Dog 1 (figure 1) Five minutes after a moderate blow there was an increase in the T_1 negativity (ekg B) from the control and the T_3 became positive. There was no further change until five and one-half hours after a second blow when the T_1 and T_2 became deeply inverted and the T_3 upright and pointed, with variation in the RS-T component (ekg G).

Dog 2 (figure 2) The first series of moderate blows did not produce

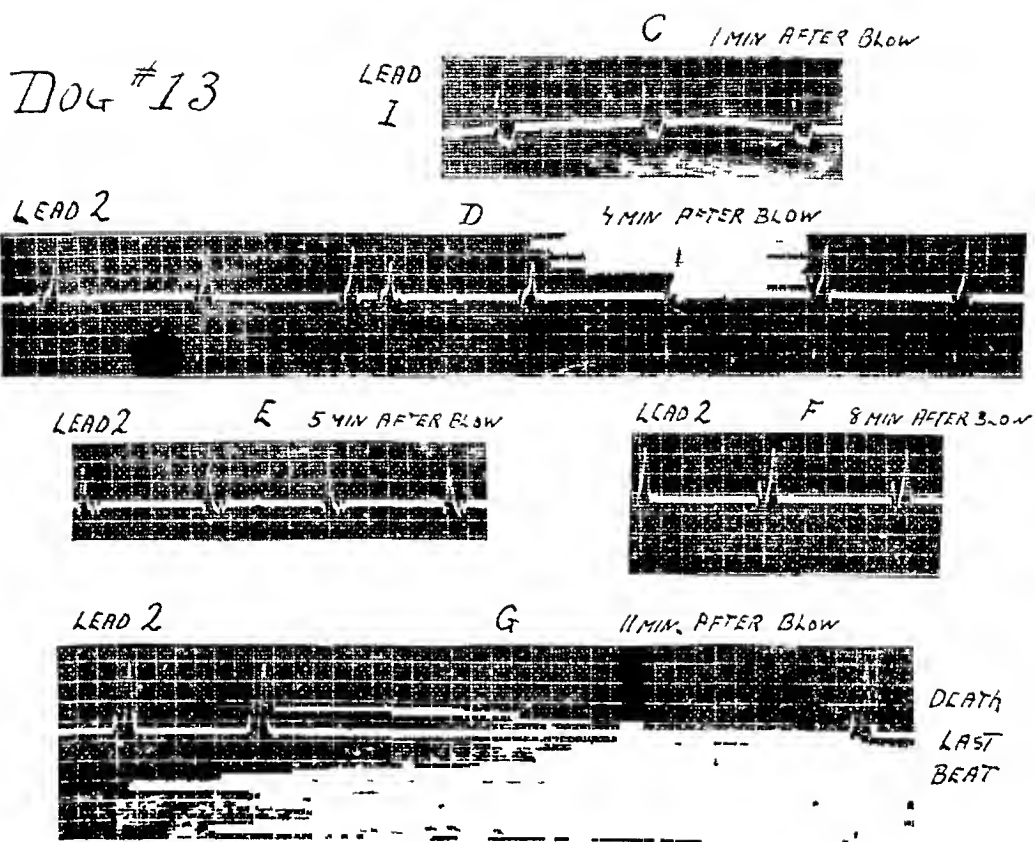


FIG 22 Dog 13

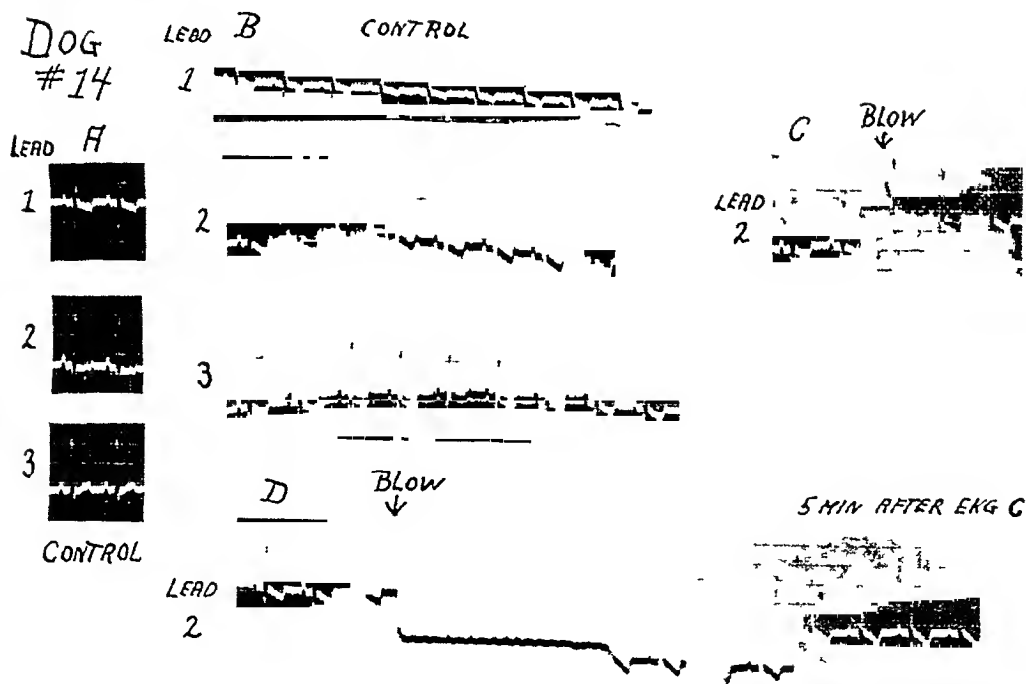


FIG 23 Dog 14

any marked deviation in the electrocardiogram from the control but five and three-fourths hours later and 45 minutes after the second series of blows the T_1 and T_2 changed to positive and the Q_1 disappeared (ekg *H*)

Dog 3 (figure 3) Five minutes after the first blow (ekg *B*) the T_3 became negative and the downward deflection of the QRS_3 in the control disappeared and became upright. These changes were not influenced by the following series of blows

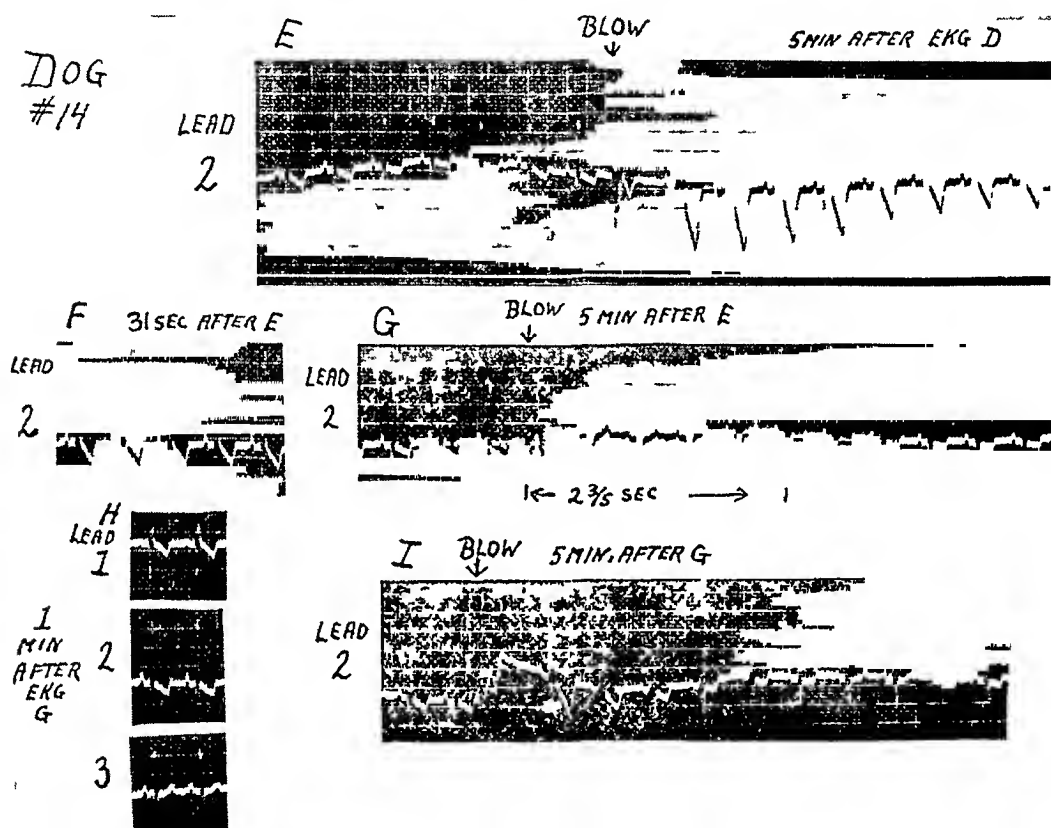


FIG 24 Dog 14

Dog 4 (figure 4) Five minutes following a heavy blow (ekg *B*) there was a change from the control to a negative T_1 , T_2 and T_3 , and one and one-half hours later (ekg *D*, Lead II) and two and one-half hours later (ekg *E*, Lead III) transient sino-aortic block appeared

Dog 5 (figure 5) Twelve seconds after a hard blow there was a change from the control in the RS-T component and (figure 5, ekg *B*) the T_1 became negative while the T_3 changed to positive, but later returned to negative as in the control. One and one-half hours later another hard blow was struck and within 10 seconds (figure 7, ekg *G*) interventricular block developed in Leads I and II with rapid decrease in the greatest deflection on the QRS wave and return to normal rhythm in Lead III. The

negative T_1 which occurred immediately following the first blow became more marked and was still present (figure 8, ekg *K*) two and one-half hours after the second blow

Dog 6 (figure 9) After four series of heavy blows there were no marked electrocardiographic changes.

Dog 7 (figure 10) After a heavy blow was delivered there were no marked electrocardiographic changes until the eighth day when the T_1 be-

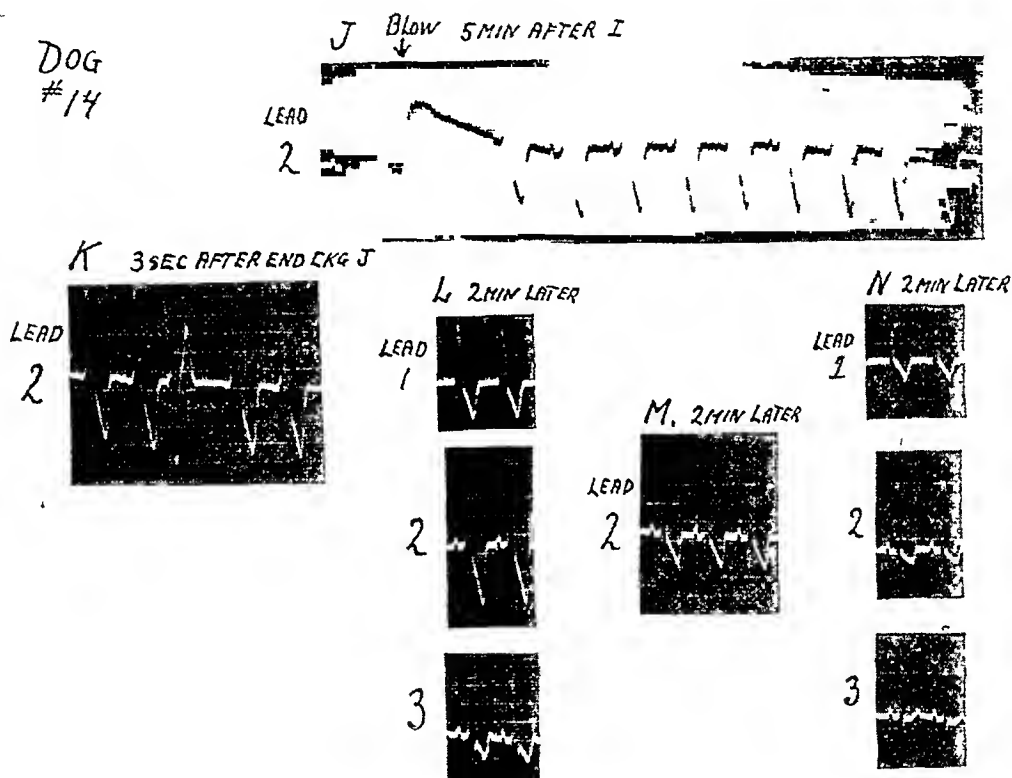


FIG 25 Dog 14

came positive (ekg *E*) and returned to negative on the fortieth day (ekg *F*) and at this time what appeared to be ventricular extrasystoles were seen by the string shadow but were not caught by the camera. The T-wave became positive in Lead II on the hundredth day (ekg *H*). There was also marked deviation of the RS-T component in the electrocardiograms taken after the eighth day (ekg *E, F, G, H*), and on the hundredth day (ekg *H*) no P-wave was seen in Leads II and III and in Lead I there appears to be a diphasic P-wave with a P-R interval of 0.24 second.

Dog 8 (figure 11) One minute after a hard blow (ekg *B*) there was a change from the control to a positive T_2 and T_3 but this was transient and on the second day (ekg *E*) the electrocardiogram was similar to the control.

Dog 9 (figure 12) There were no marked changes from the control.

in the electrocardiograms taken following the blow until the seventh day (ekg *D*) when the T_2 and T_3 were positive

Dog 10 (figure 13) One minute after the blow the electrocardiogram *B* revealed ventricular fibrillation which ended in death 16 minutes later (figure 14, ekg *M*)

Dog 11 (figure 15) Two minutes after the blow (ekg *B*) there is an absence of the P-wave, evidently an auricular paralysis with an idio-ventricular rhythm Three minutes after the blow (ekg *C*) there is an idio-

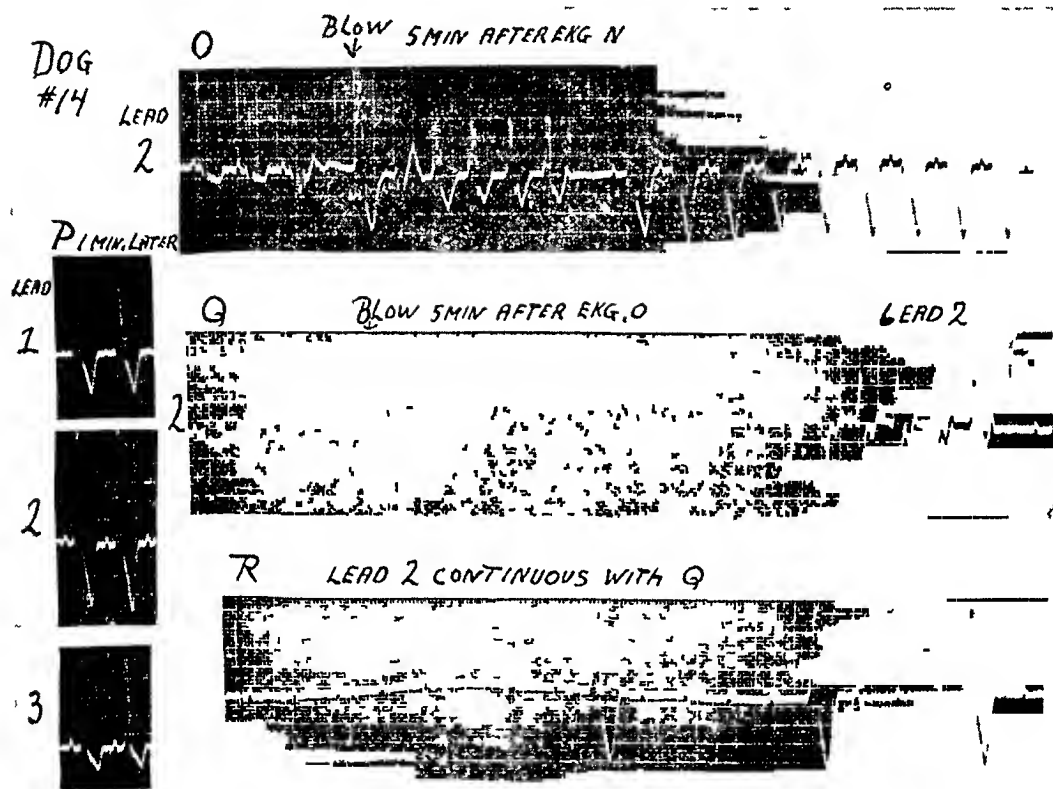


FIG 26 Dog 14

ventricular rhythm and in Lead I the P-wave appears following the QRS wave, and also in the first part of Lead II, and in the fourth complex the P-wave begins to be gradually incorporated in the QRS wave until the P-wave has completely disappeared and permanent auricular paralysis established with monophasic ventricular complexes of the dying heart (figure 16, ekg *D*, *E*) Death occurred 21 minutes after the blow (figure 17, ekg *I*)

Dog 12 (figure 18) One minute after a blow the electrocardiogram changed from the control to (ekg *B*) an interventricular block, which in Lead I is shown to be transient and suddenly in the third complex the QRS wave greatly decreases in magnitude and the T-wave becomes inverted until in four minutes the complexes in all leads (ekg *C*) have returned to

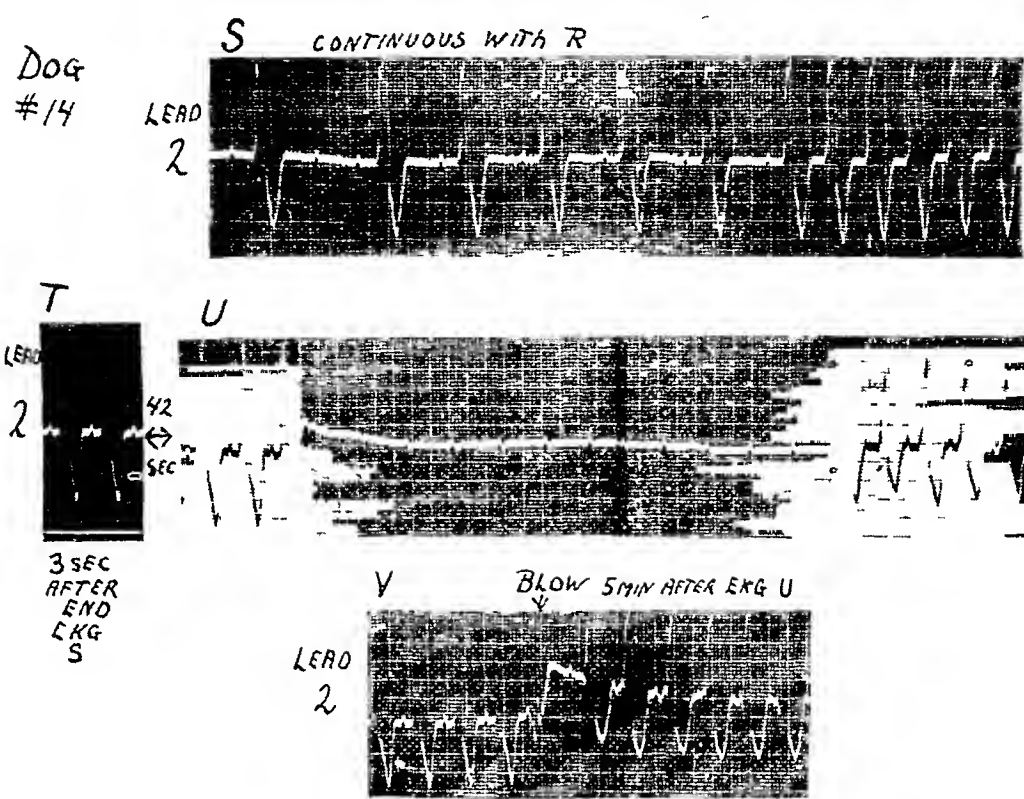


FIG 27 Dog 14

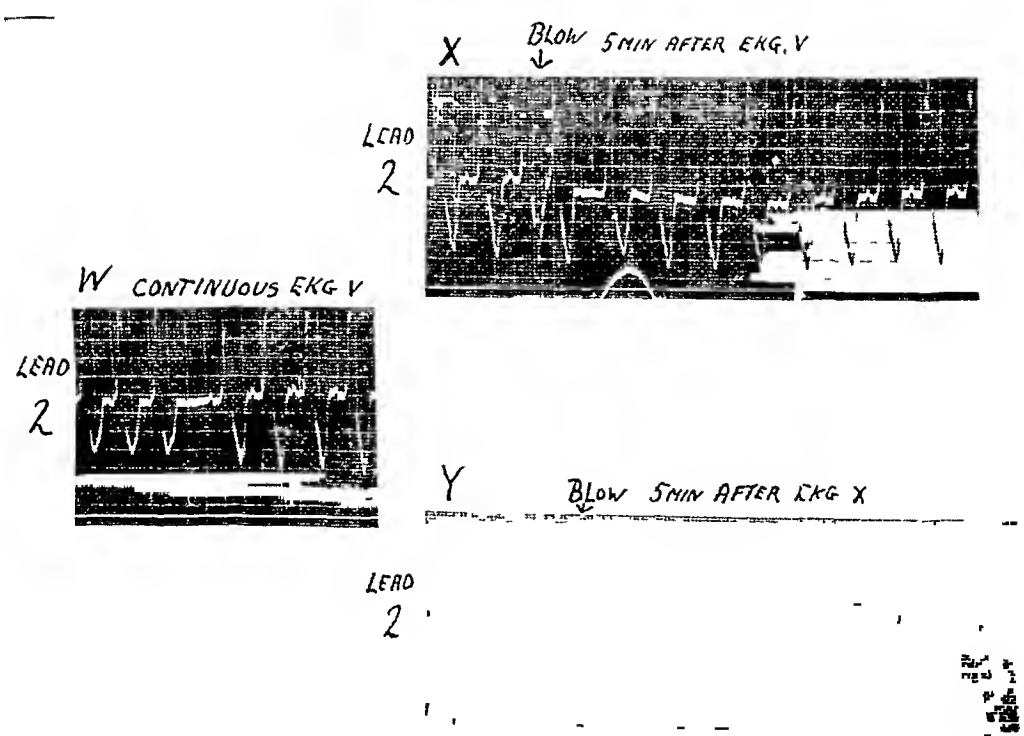


FIG 28 Dog 14

the type seen in the control (ekg *A*) Another blow was struck and again within one minute (figure 19, ekg *D*) interventricular block occurred and in nine minutes returned to the normal rhythm (ekg *E*) seen in the control Another blow was struck and one minute later (ekg *F*) an idio-ventricular rhythm was established with an absence of the P-wave, with slow undulating waves of the base line Three minutes after the blow (ekg *G*) the idio-ventricular rhythm was still present with some changes in the character of the QRS waves and the appearance of a negative pointed T_1 wave Thir-

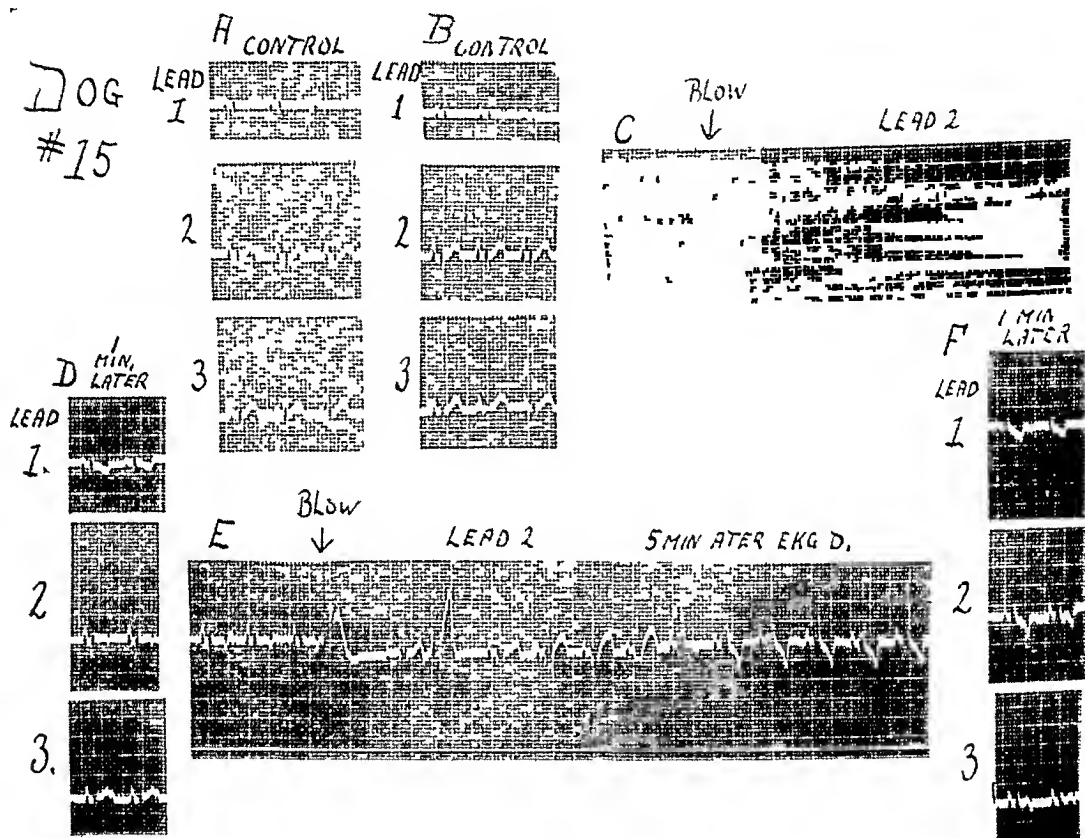


FIG 29 Dog 15

teen minutes after this blow (figure 20, ekg *H*) there was a return to the normal rhythm of the control and sino-auricular block in Lead I One minute after another blow (ekg *I*) idio-ventricular rhythm appeared with no P-waves and slow rhythmic undulations of the base line and after four minutes there was (ekg *J*) auricular paralysis with monophasic ventricular complexes and death at this time

Dog 13 (figure 21) While Lead I of the electrocardiogram was being taken (ekg *B*) a blow was delivered with the string protected and in 42 seconds interventricular block with gradual slowing of the rate until, in 126 seconds all signs of a P-wave disappeared with an idio-ventricular

hythm One minute after the blow (figure 22, ekg C) the rhythm was the same but the ventricular complexes changed in character and after four minutes (ekg D) there was a complete heart block with idio-ventricular rhythm, an occasional ventricular extrasystole, and pairs of rhythmic P-waves separated by long intervals of auricular paralysis and idio-ventricular rhythm with diphasic ventricular complexes until death in eleven minutes (ekg E, F, G)

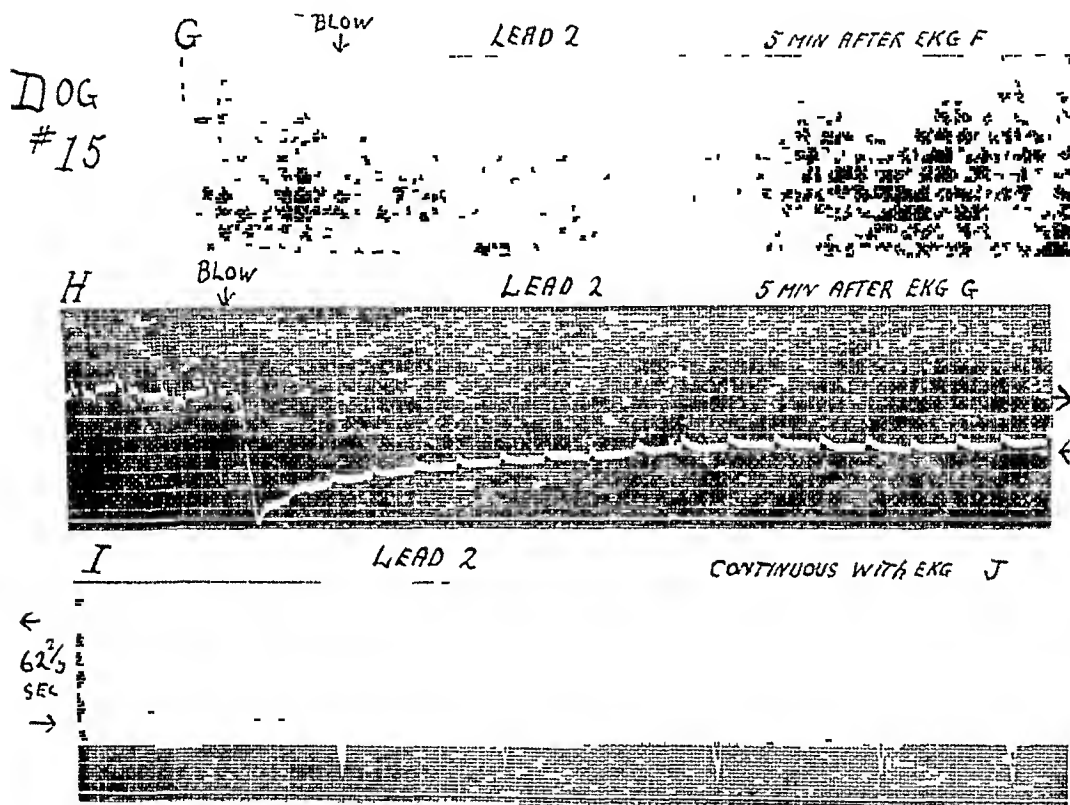


FIG 30 Dog 15

Dog 14 (figure 23) Two blows were delivered while Lead II of the electrocardiogram was being recorded (ekg C, D) without marked changes. The blow was repeated (figure 24, ekg E) in the same manner and in 0.6 second and with the next complex, interventricular block occurred which was transient and (ekg E, F) returned to the normal rhythm (ekg G) of the controls in five minutes. At this time another blow was struck while Lead II of the electrocardiogram was being taken (ekg G). The next beat after the blow revealed a change to an upright T-wave, change in the RS-T component and the Q-wave of the QRS complex disappeared and the initial deflection of the ventricular complex became upright. These changes were transient and within 2.6 seconds the QRS wave returned to the former character and the T-wave became negative. One minute later (ekg H)

there was a return to the normal rhythm of the controls Five minutes later (ekg *I*) the blow was repeated while Lead II of the electrocardiogram was being taken and the next complex revealed a transient interventricular block with return to the control rhythm in three seconds Five minutes later another blow was struck (figure 25, ekg *J*) while Lead II of the electrocardiogram was being taken and after 0.8 second of cardiac standstill interventricular block developed, with an occasional ventricular extrasystole (ekg *K*), which was transient (ekg *K, L, M, N*) and returned to the nor-

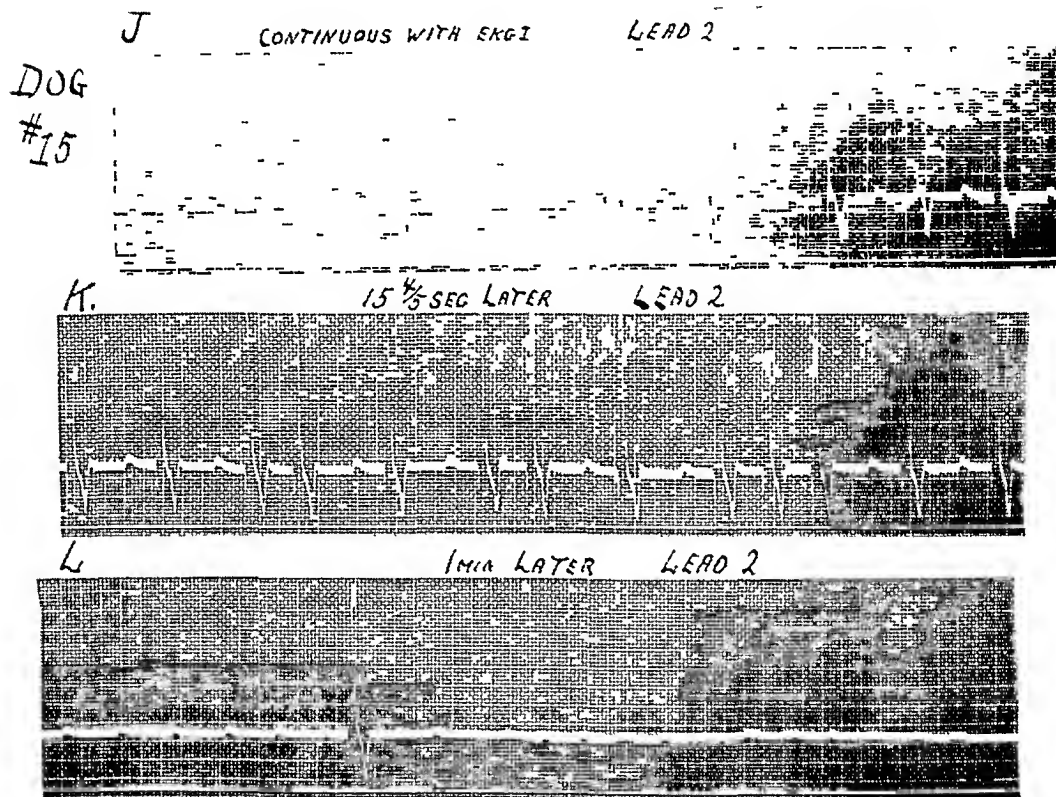


FIG 31 Dog 15

mal control rhythm (figure 26, ekg *O*) 11 minutes after the blow, at which time the blow was repeated under like circumstances (ekg *O*) Immediately ventricular tachycardia developed and in 2.2 seconds a P-wave appeared with interventricular block (ekg *P*) Then after another five-minute interval another similar blow was struck (ekg *Q*) which was followed by 0.8 second of cardiac standstill, then by ventricular tachycardia with various types of diphasic ventricular complexes, and after 6.8 seconds a P-wave appeared with a complete heart block and only occasional idioventricular complex (ekg *Q, R*) which became more frequent until, after six seconds (figure 27, ekg *S*) there is 2 to 1 block and in seven seconds interventricular block, changing in 10.4 seconds to ventricular tachycardia,

then back to interventricular block (ekg *T*) About 42 seconds later there was complete heart block with ventricular standstill followed by interventricular block again (ekg *U*) Five minutes later another blow was delivered while (ekg *V*) the interventricular block was present without marked changes Five minutes later when this was repeated (figure 28, ekg *X*) the interventricular block disappeared and ventricular tachycardia occurred for five complexes, after which there was a return to interventricular block, with occasional changing back and forth between these rhythms (ekg *W*, *Y*)

Dog 15 (figure 29) A blow was delivered while Lead II of the electrocardiogram was being taken (ekg *C*), which was followed by one ventricular extrasystole with immediate return to the normal control rhythm (ekg *C*, *D*) This was repeated five minutes later with transient interventricular block of the right and left branches of the Bundle of His and one ventricular extrasystole, each change being separated from the other by a normal complex (ekg *E*) and in one minute the rhythm of the control returned (ekg *F*) After another five-minute interval a similar blow was given and again (figure 30, ekg *G*) transient interventricular block immediately developed to return to the normal control rhythm in five minutes when the final blow was delivered, followed by complete heart block and ventricular standstill for 73 seconds (ekg *H*, *I*) after which 5 to 1, 4 to 1, 3 to 1, and 2 to 1 block occurred (figure 31, ekg *J*) The idio-ventricular complexes appear in groups of two's and three's and one minute later the P-waves became very small in amplitude (ekg *L*), finally disappearing with one last diphasic idio-ventricular complex, then death

DISCUSSION AND COMMENT

The most frequent electrocardiographic changes were in the T-waves and the RS-T components and occurred in 10 of the dogs* In the first series of experiments with Dogs 1, 2, 3, 4 and 5, these changes occurred during a period varying from a few minutes to a few hours, after various degrees and types of chest injuries Since all the electrocardiograms were taken with the dogs in the same position, the chance of error was removed Only two of these five dogs showed abnormal lesions of the heart, Dog 1 with hemorrhage into the mediastinal space and cusps of the pulmonic and mitral valves and Dog 5 with thickening and hemorrhage into the pericardium and into the tissue about the base of the heart While three of the dogs had hemorrhage into the lung, two others with more marked T-wave and RS-T component changes did not show this lesion and therefore these changes were not attributed to generalized anoxemia, neither can they be attributed to increase of the fluid in the pericardial sac because in none of the five dogs was this found to be present The gross and microscopic examina-

* Since this article has been written additional experiments of the same type have been performed and in one dog, we were able to produce auricular fibrillation following external trauma to the chest

tion of the hearts of these dogs revealed them to be normal except for slight hemorrhage into the valve cusps of Dog 1. In Dog 4 there were no abnormal lesions found.

The second series, Dogs 6, 7, 8 and 9, were not killed following the external chest injury. Dog 6 lived a few hours, then died from hemorrhage into both lungs. The autopsy revealed a rupture of the diaphragm and a tear in the pericardium with a small amount of hemorrhage into the pericardial sac, but there were no electrocardiographic changes observed.

Dog 7 was disregarded because following sudden death, upon the one hundred and twenty-first day, there was found some thickening of the coronary artery which was not traumatic but could possibly have caused electrocardiographic changes.

Dog 8 showed immediate T-wave and RS-T component changes, as did also Dog 9 on the seventh day. Dog 8 died on the third day and the autopsy revealed a small tear in the pericardium. Dog 9 died on the sixteenth day and the autopsy revealed congestion of the lungs and heart failure cells. Evidently in Dog 9 heart failure had been present before death, although in neither case were any abnormal lesions found in the myocardium, and it is possible that this failure may have been due to some serious type of arrhythmia which was not present at the time the electrocardiograms were taken.

The third series, Dogs 10, 11, 12 and 13, were struck heavy blows to the chest in an attempt to produce death in as short a time as possible. In Dog 10 ventricular fibrillation was produced with death in sixteen minutes, in Dog 11 idio-ventricular rhythm with auricular paralysis occurred with death in 21 minutes. The autopsies failed to reveal any abnormal lesions. Dog 13 had immediate changes in the T and QRS waves and the RS-T component and later developed a heart block, interventricular block, and finally auricular paralysis with idio-ventricular rhythm which eventually caused death. The autopsy in this case revealed hemorrhage into the tissue about the base of the heart, into the pericardial sac with slight sub-pericardial and myocardial hemorrhage of the wall of the right and left auricles. These three dogs in the third series died as a result of fatal arrhythmias and demonstrated the possibilities of sudden death from external chest injuries with insufficient pathology to explain these arrhythmias or to be considered as a cause of death. Dogs 12, 14 and 15 demonstrated that many various types of arrhythmias occur immediately and in a very short time return to normal rhythm but with each successive chest injury the arrhythmia remained for an increasing period.

In the fourth series, Dogs 14 and 15, the right and left vagus nerves, the right and left superior and middle cervical ganglions and the spinal cord were cut before any of the blows were delivered. This was done to avoid the possibility of extra-cardiac lesions producing the electrocardiographic changes. Although the first two hard blows struck Dog 14 did not pro-

duce electrocardiographic changes, almost all the arrhythmias, T-wave and RS-T component changes seen in the other dogs were reproduced in these two animals. Similar traumatic lesions outside the heart, such as contusion and hemorrhage of the lungs, rupture of the liver and diaphragm, were produced in these dogs which would seem to indicate that the changes seen in the dogs of the other series were not due to injury outside the heart.

Considering the entire 15 animals the most frequent lesion produced was injury of some type to the lung. This occurred in eight dogs, following both severe and mild blows to the chest. Rupture of the liver occurred twice, and rupture of the diaphragm once. These lesions, together with hemorrhage into the mediastinal space, were the chief lesions found outside the heart. The most frequent cardiac lesions were sub-endocardial and sub-pericardial hemorrhage which occurred four times, as did also pericardial injury and tear with or without free blood in the pericardial sac. With the exception of hemorrhage into the valve cusps, which occurred twice, and hemorrhage into the tissue about the base of the heart, no other lesions were found. In three dogs there were no lesions of any kind and, since the electrocardiographic changes are sudden and transient, these changes may be considered due to edema of the myocardium and the various parts of the conduction system. These changes are also similar to those following experimental coronary artery occlusion and injury to the Bundle of His, in dogs. It is evident that mild and severe blows produce various types and degrees of electrocardiographic changes and the tendency is for the heart to return to normal within a very short time. On the other hand the same degree of blow may produce a fatal arrhythmia. It is also evident that there need be no injury to the chest wall, which occurred only in the two dogs of the last series, to produce both electrocardiographic changes and abnormal lesions of a serious nature.

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ADRENAL CORTICAL TUMOR, A REPORT OF FOUR CASES *

By CHARLES H. LAWRENCE, M D , F A C P , *Boston, Massachusetts*

IN his paper on tumors of the suprarenal cortex read before the Staff of the Mayo Clinic in 1933, Kepler¹ cites the following quotation from Rowntree and Ball

"We may say that there are various types of tumors of the suprarenal gland, resulting in a large variety of clinical symptoms and syndromes, many of which are difficult to explain adequately in the present state of knowledge. Correlated clinical, pathological and chemical studies are urgently needed." The following four case reports, which more or less imperfectly meet these specifications, seem worth adding to the literature

Case 1 F R , female, 13 yrs 10 mos , first seen November 1, 1928

Family History Father, mother, two sisters living and well. No family history of endocrine disease. Mother's catamenia irregular and profuse. One sister hypomenorrheic through adolescence, normal since.

Past History Measles, mumps, chicken pox, pertussis in childhood. Tonsillectomy in childhood. Appendectomy at 11 for acute appendicitis.

Present Illness Menarche at 10 yrs 8 months. During the next nine months menstruation was regular every 28 days, lasted four to five days, amount regarded as normal, no pain. In June 1926, patient menstruated normally but had not menstruated since, an interval of 17 months. During the first six months of amenorrhea there was no change in her general condition, and little attention was paid to the lack of menstruation.

In June 1927, patient's mother noted beginning masculinization. The voice became deeper and hoarser, and coarse dark hair appeared on arms, legs, abdomen, cheeks and chin. Both voice change and hair growth increased steadily. The patient's general health remained excellent. She denied any other symptoms than those enumerated.

Physical examination showed a well developed and nourished girl. The body contour was normally feminine. There was moderate acne of the face, chest and back. There was moderate hypertrichosis of cheeks, chin, and upper lip, and a considerable growth of coarse, dark hair on the arms and legs. The pubic hair extended upward to the navel. The labia were slightly hypoplastic, the clitoris was slightly larger than normal. Rectal examination disclosed a rather small uterus, but no other pelvic abnormality. Abdominal examination revealed no abnormality. The physical findings were otherwise normal.

Laboratory Findings The urine was normal as was the blood morphology, and chemistry. Renal function (phenolsulphonephthalein elimination) was 59 per cent in two hours. Basal metabolism was plus 3 per cent, with normal pulse rate, blood pressure and temperature. Roentgen-rays of the skull, kidneys and urinary tract showed no pathology. Eye grounds and visual fields were normal. Pelvic ex-

* Received for publication July 28, 1937

From the Endocrine Clinic of the Boston Dispensary

amination with anesthesia showed no abnormality other than slight uterine hypoplasia

Course The sudden cessation of previously normal menstruation, and the masculinization suggested either tumor of the adrenal cortex, pineal tumor, or tumor of the ovary (Basophilic adenoma of the pituitary was unknown at that time) No diagnosis could be definitely established, however, and the patient was kept under observation for a year During this period no change occurred in the clinical picture there was no loss of weight, and the blood pressure, observed repeatedly, remained perfectly normal Injections of "Amniotin" and "Estrogen" were without demonstrable effect

At the end of a year, the patient was seen in consultation by Dr D L Jackson, who confirmed the physical findings already noted In his opinion, sclerosis of the ovarian cortices was the most probable diagnosis, and at the request of the patient, an exploratory operation was performed, December 5, 1929

Operative Findings The cervix was small Curetting the uterus yielded no endometrium, in spite of the fact that a serrated curet was used On opening the abdomen, the uterus was found to be small and retroverted The Fallopian tubes were normal The ovaries were smooth with thickened cortices Both ovaries were split, and were found packed with small cysts, which were evacuated The cortex was then peeled The left kidney and adrenal body were normal to palpation There was a question as to whether the right adrenal gland could be felt, but no pathological condition could be demonstrated The wound was therefore closed Pathological report on the curettings No endometrial tissue found Specimen from ovary—simple cyst, and numerous unripe follicles

The patient made an uneventful recovery There was no change in the clinical picture She was seen at intervals of three to six months during the next six years, but no significant development occurred until September 1934 (nearly five years after operation), when she began to develop moderate dyspnea and palpitation on vigorous effort Examination at that time showed the heart to be normal, but the resting pulse rate had increased to 96 per minute, and the blood pressure had risen to 140 systolic and 80 diastolic The retinal arteries were slightly narrow, the veins moderately over full Blood and urine were normal The breasts had become atrophic, and there was marked hair growth around the areolae Abdominal examination was negative Intravenous pyelograms showed that the right kidney was larger than the left, and its border was somewhat irregular The pelves, infundibulae and calices filled well, but the upper calix of the right kidney was depressed There were no other abnormal findings Neither Dr Prather nor Dr Morrison who together conducted the examination, felt that there was enough evidence of adrenal tumor to justify operation They advised further observation

In April 1935, the patient's condition was essentially unchanged, the slight hypertension persisted, and abdominal palpation gave a sense of an indefinite mass in the right flank not apparently connected with the liver Repetition of the pyelogram showed, on the right side, numerous small areas of calcification scattered between the levels of the first lumbar vertebra and the tenth rib posteriorly, and a suggestion of the rounded outline of a mass overlying the upper pole of the right kidney

On the basis of these findings, the diagnosis of tumor of the right adrenal gland seemed established, and after consultation with Dr Prather, it was decided to operate after preliminary radiotherapy had been completed There was no significant change in the patient's condition up to the time of operation, July 25, 1935 At operation, a rounded, encapsulated tumor on the right adrenal 12.5 by 10 by 8 cm was removed It was completely encapsulated, fairly homogeneous, brown, opaque and soft Scattered through it, particularly near the periphery, were bony spicules Because of the size of the tumor it was necessary to remove both the right kidney and

the right adrenal gland with it. The latter showed a slight thickening of the cortex, and was otherwise normal. The kidney was normal.

The patient showed a fall in blood pressure to 100 systolic and 70 diastolic, 24 hours after operation. Eschatin was administered during the next three days, and gave a prompt response. Thereafter, the blood pressure varied between 120 and 130 mm systolic with a diastolic of 80 mm. The patient made an uneventful recovery.

Within three weeks after operation her voice showed a definite return to the feminine timbre and within two months was completely restored to its former quality. The patient began to menstruate on September 1, and flowed four days normally, without pain. Thereafter she has continued to menstruate normally and regularly. One year after operation examination showed some gain in weight and marked regression of the hypertrichosis. A recent report states that the abnormal hair growth has now practically disappeared.

COMMENT

The outstanding feature of this case is the long duration of the syndrome before its cause could be identified. In November 1928, the masculinization was sufficiently impressive to leave no doubt that there was serious disturbance of endocrine function, but a rather complete diagnostic study afforded no evidence sufficient to identify the gland at fault. Such evidence as there was suggested pathology of the adrenal cortex or ovary rather than of the pituitary, possibly because Cushing's paper² had not yet appeared to emphasize the similarity of the clinical pictures produced by pituitary basophilism and tumors of the adrenal cortex. In retrospect, a number of features characteristic of pituitary basophilism are lacking in this case. There was no "rapidly acquired, peculiarly disposed and usually painful adiposity," no kyphosis, no "plethoric appearance of the skin with purplish lineae atrophicae," no vascular hypertension for six years after the clinical picture was fully established, no erythremia, and no backache or fatigability. The patient's health, as that term is usually understood, was excellent at all times, and she attended school and college during the years that she was under observation, taking part in all the usual activities.

The absence of all these characteristic symptoms is worth remarking, since some or all of them were present in the other patients described in this report. Why they should have been lacking in this patient cannot be explained, nor is speculation profitable. Another feature worth emphasizing is the definite masculinization of the voice, and its return to normal after removal of the tumor. This feature is not mentioned by Cushing as characteristic of pituitary basophilism,² and although it is not always present in the adrenocortical syndrome, it should be of considerable diagnostic value when it exists.

The third feature which justifies comment is the evidence afforded by the exploratory operation performed one year after masculinization had become well established. Unquestionably the tumor of the right adrenal cortex was present at that time, but it could not be palpated through the abdominal incision. It must be concluded that it was very small at that time (though the difficulty of palpating the adrenals through a median ab-

dominal incision is considerable) and therefore that even very small tumors of the cortex are capable of causing marked masculinization. The condition of the ovaries is also interesting in view of the rapid reestablishment of normal menstruation following the second operation. At the first laparotomy they were found to be sclerosed and cystic, and were subjected to a considerable degree of surgical trauma, yet they promptly reassumed their normal function six years later when the inhibiting tumor was removed. It is, therefore, obvious that the organic pathologic changes discovered at the first operation were not the primary cause of the amenorrhea.

Case 2 A married woman, 24 years old, entered the hospital March 9, 1936, in coma.

Family History Father, mother, and four siblings were living and well. The maternal grandmother was allergic.

Past History No serious illnesses, no operations. As an infant, the patient was allergic to eggs, and in recent years to grass pollens, the symptoms being controlled by desensitization treatment.

Menstruation began during her fifteenth or sixteenth years, and was regular and normal until 1933, when she developed functional menorrhagia. At that time she showed a moderate secondary anemia, a basal metabolic rate of minus 21 per cent, normal blood sugar, a rather flat sugar tolerance curve. Physical examination showed slight symmetrical enlargement of the thyroid, hyperplastic breasts, and a small uterus. Three months' treatment with Antutrin S, 200 R U every other day during the intermenstrual intervals, restored menstruation to normal, and it remained so until the present illness. The patient's health had been good until a week before entering the hospital, though her parents thought she seemed more tired than usual for several months before its onset.

Present Illness February 29, 1936, while driving her car she had a brief attack of blurred vision and felt rather faint. She was, however, able to drive her car home, and after luncheon and a short rest, felt as well as usual. The next day she woke at seven, went to her sister's room for a time, and then returned to her bed for another nap. At noon her mother found her still "asleep," perspiring profusely. She was roused with considerable difficulty, and her speech was a bit incoherent. She drank a glass of orange juice, and an hour later seemed as well as ever, though she did not remember having gone to her sister's room. During the following week she felt as well as usual, but on March 9 her husband, when he went to waken her in the morning, found her in coma, and was unable to rouse her. She was seen immediately by Dr. Halsted, who found, as the only abnormal physical sign other than the coma, a palpable tumor in the left upper quadrant of the abdomen. She was taken immediately to the Faulkner Hospital, where I saw her an hour later.

Physical examination showed a well developed and nourished young woman, completely unconscious. Her pulse was not greatly accelerated, temperature normal, blood pressure normal. The pupils reacted to light, the retinæ were normal, there was no choked disc, no stiffness of the neck, no abnormal reflexes. The knee-jerks and plantar reflexes were diminished but present. The heart and lungs were normal. Inspection of the abdomen showed that the left upper quadrant of the abdomen was more prominent than the right, and palpation disclosed a large mass there, extending from beneath the costal margin to about the level of the umbilicus, and from the midline outward into the flank. The mass felt resilient, and smooth. Determination of the blood sugar showed 44 mg per 100 cc of blood. The plasma combining power for carbon dioxide was 51 volumes per cent. The urine showed four plus acetone.

The patient was given one liter of 10 per cent glucose solution. She regained consciousness after receiving about 50 c.c. and was well oriented and replied intelligently to questions before the infusion was completed. She stated that she had been aware for two or three weeks that the left upper quadrant was "fuller" than the right, but had thought, since she felt well, that she was merely growing fat.

The patient was seen in consultation by Dr. E. L. Young, Jr. Because of the hypoglycemia and the size of the tumor, he felt that it was probably a pancreatic cyst, and advised exploratory operation. This was done six hours later. On opening the abdomen a mass the size of a large grapefruit, bluish red in color, and highly vascular, was encountered. It was encapsulated, and across its surface ran a network of large veins. It extended backward to the posterior abdominal wall, to which it seemed fixed. There was no pedicle. A trocar was introduced and intense suction applied, but no fluid obtained. Removal by the anterior approach was obviously impossible, so a small specimen was excised with the electrocautery, and the wound closed. The pathological report on the specimen was as follows: "Carcinoma, growing with moderate speed, originating in an endocrine gland. Whether the tumor is arising from the cells of the islands of Langerhans or from the adrenal cortex cannot be positively determined from present sections. Further studies as to cell origin are being carried out." As a result of those further studies, in which several pathologists collaborated, it was then the consensus that the tumor arose from the adrenal cortex.

The patient made an uneventful though slow recovery from the operation. The fasting blood sugar, determined daily for 18 days, varied between 101 mg. and 41 mg. per 100 c.c. Readings of 60 mg. or less were obtained six times during that period. These low readings were not always accompanied by clinical symptoms of hypoglycemia. The blood counts showed nothing abnormal. Hormone assays March 23 were negative for both prolactin and estrin. The patient continued to menstruate, however, for two months, but since May 27, 1936, has been amenorrheic. Post-operative roentgen-ray treatment was begun March 23, and continued until July 10, utilizing coutard dosage 258 R units. Total R units 3,200. During this treatment, she had no major hypoglycemic attacks, though she occasionally felt dizzy on awakening. Prompt relief was obtained by drinking a large glass of orange juice. Between July 10 and October 13 the attacks of hypoglycemic coma recurred frequently but irregularly, but always responded to intravenous injections of 10 per cent glucose solution. The blood pressure showed a definite upward trend, averaging during October, 150 mm. systolic and 90 mm. diastolic. A mild acne, present at the time of operation, became extremely severe, involving the entire face, the neck, chest and back, and there was marked acanthosis of the axillae. The tongue had become thickened and fissured, and the face, neck and shoulders showed marked thickening of the skin and subcutaneous tissue. Blood non-protein nitrogen and chlorides were normal, and the blood sugar normal when determined. Hormone assays were again negative for both prolactin and estrin. Roentgen-rays of the skull, chest, colon (with barium enema) and kidneys (intravenous pyelogram) showed no evidence of metastases. The mass extended to the top of the fourth lumbar body, and across to the right of the spine. The colon was pushed forward and downward. It was impossible to make out the kidney outlines, but the dye reached the bladder in normal time and in normal concentration.

On October 13, a second attempt was made to remove the tumor, Dr. William E. Ladd operating, by the transabdominal route. Again it was found impossible to remove the growth. The left kidney was identified in close relation to the tumor mass, and the diagnosis of a tumor of the suprarenal cortex seemed confirmed.

Thirty-six hours after operation the patient's temperature rose suddenly and rapidly to 104.4° (rectal), the pulse rate rose from 120 to 180, and the blood pres-

sure fell rapidly to 70 mm systolic and 50 mm diastolic. She became comatose, reviving after intravenous glucose and adrenalin 1-1000 subcutaneously. No evidence of infection could be found. Twelve hours later she was much improved, and on the third day after operation showed a remarkable change for the better. The pulse rate had fallen to 88, temperature 101°, blood pressure normal. During the next two weeks she showed marked general improvement, especially in the skin condition. The subcutaneous thickening almost disappeared, the acne and acanthosis diminished markedly. She left the hospital November 7 in good condition.

During the next two months the patient's condition again grew slowly worse. The acne, acanthosis and subcutaneous thickening increased, though never to their former intensity. The hypertension became more marked, often reaching 190 mm systolic and 120 mm diastolic and occasionally going higher, and the attacks of hypoglycemic coma recurred with increasing frequency. Edema of the lower legs appeared, and shifting dullness in the abdomen could be demonstrated from time to time. During the attacks of coma the patient often became rigid, assuming a posture like that of decerebrate rigidity. At other times the hypoglycemic symptoms consisted merely of perspiration, tingling of the tongue, and moderate analgesia. During one of these mild attacks she was given, instead of glucose solution intravenously, 0.1 cc of adrenalin 1-1000 subcutaneously. The symptoms disappeared with dramatic promptness. Thereafter it was found that a slightly larger dose (0.3 to 0.5 cc) was equally efficacious in the attacks of coma, injection being followed promptly by return to consciousness, so that the patient was able to swallow orange juice within 15 or 20 minutes after the injection.

Despite the general downward progress of the disease, the patient showed surprisingly little loss of strength, and on Christmas day was able to join in practically all the family festivities. Early in January, however, she developed moderate abdominal distention, and rather frequent attacks of headache, and it was decided to use radium treatment. After consultation with Dr. Barringer and Dr. Ewing, of the Memorial Hospital, New York, she was therefore admitted to that institution on January 14, 1937, for treatment. She tolerated radium treatment well, and returned to her father's home to carry on restraint dosage of roentgen-ray. Again irradiation of the tumor was followed by cessation of the hypoglycemic attacks.

On April 9, 1937, the patient complained that during the past week her vision had been failing, especially in the right eye. Ophthalmological examination (Dr. Whitney) showed "Right eye: Disc margins clearly defined, arteries sclerotic, pinching the veins at their crossings, and veins tortuous and distended due to arterial interference. No hemorrhages seen. Left eye: Arteries sclerotic, veins normal size." Dr. Whitney's impression was that the failure of vision was due to obstruction of the venous circulation in the retinae, and also in the central vessels.

The patient's general condition showed little change. The blood pressure varied between 140 and 160 mm systolic, and 90 and 100 mm diastolic. The abdominal distention grew more prominent. There was variable shifting dullness, and intermittent edema of lower legs and ankles. Hypoglycemic attacks of variable intensity, always responding to adrenalin, recurred two or three times weekly. It was, therefore, decided as a last resort to treat her with the extremely powerful roentgen-rays now available at the Huntington Hospital. On admission to the hospital the patient was found to have considerable fever which subsided by lysis in three days. During her stay in the hospital this sudden rise in temperature followed by a lysis recurred twice. Roentgen-ray of the chest gave evidence of metastases in the right lung. The patient had several hypoglycemic episodes while in the hospital but after completion of the treatment they did not recur. Hormone assays of specimens obtained during hospitalization were negative for prolactin and estrin, but positive for the male hormone, quantitation showing between 15 and 20 bird units present.

She grew weaker and more emaciated, developed a harassing cough and marked anorexia, so that it became almost impossible to furnish an adequate amount of carbohydrates. In spite of this deficiency, however, she did not have any more hypoglycemic attacks.

Death came apparently from general exhaustion on July 8. Unfortunately permission for autopsy could not be obtained.

COMMENT

The outstanding symptoms in this patient contrast sharply with those of the first. In one, symptoms were fully established before the tumor could be palpated during laparotomy, while in the other, the growth had reached such size as to cause visible tumor of the abdomen before severe symptoms appeared. This fact alone would suggest that the two tumors were different in nature.

Even more convincing, however, is the hypoglycemia encountered in association with the growth. The patient's blood sugar was normal when it was determined three years previously, and she had had no symptoms suggesting hypoglycemia until 10 days before the tumor was discovered. It is hardly likely, therefore, that the former antedated the latter. The mechanism by which an adrenal cortical tumor produces hypoglycemia is far from clear, and a careful search of the literature discloses no record of a similar association. In fact, hyperglycemia and glycosuria seem to represent the usual disturbance of carbohydrate metabolism in both the adrenocortical syndrome and pituitary basophilism (Cushing,² and Kepler et al.^{1,3,4}) and hypoglycemia has been reported in human adrenal insufficiency by McLean.⁵ Britten and Silvette⁶ found diminution in blood sugar and liver and muscle glycogen in dogs, cats, rabbits, guinea pigs and rats after adrenalectomy, and produced hypoglycemic convulsions and death by removing the adrenals of opossums and marmots. It is not clear, however, whether it is the loss of cortex or medulla which produced these results.

Equally obscure is the mechanism by which small doses of adrenalin relieved the hypoglycemic attacks in this patient. The fact that it did, however, suggests that the low levels of blood sugar were due not to an exhaustion of glycogen reserves, but to an interference with its mobilization.

The further features of special interest are the amenorrhea and atrophy of the breasts, without positive masculinization, the absence of prolan and estrin from the urine, the apparent beneficial effect of irradiation upon the hypoglycemic attacks, and the changes in the skin.

The latter merits, perhaps, special consideration. The skin of the face, which had previously been normal, became thickened, dusky red, and literally covered by small acne papules and pustules. The same process extended downward over the neck, shoulders, chest and back, and in the axillae the hyperplasia of the epidermis was so severe as to produce small lobulated tumors. Following irradiation of the tumor temporary remission of the skin condition occurred.

It is, perhaps, not absolutely certain that the tumor in this case arises from the adrenal cortex. However, the anatomical findings at the second operation and the general agreement of opinion among the pathologists who have examined the sections obtained seem sufficient to eliminate all but the faintest chance that it arises from any other organ. The endocrine character of most of the patient's symptoms suggests a hyperfunctioning gland rather than a non-secreting malignant growth, and the presence of male hormone in the urine is characteristic.

Case 3 A white female of 30 years, single, American, school teacher. She was referred to the Diagnostic Hospital, April 20, 1934, by Dr. Eugene McCarthy of Rumford, Maine, because of blurred vision, of 18 months' duration, polyuria and nocturia for nine months, and amenorrhea for eight months. Dr. McCarthy's history also showed that she had felt unduly fatigued for several years, had "bruised easily, and had noticed an increasing growth of hair on her face for the past year." Polyuria and nocturia, but no polydipsia, had bothered her for about nine months before admission.

Family History One brother died of "sugar diabetes" at the age of fourteen. Two brothers and her father and mother are living. The latter has some kidney trouble.

Past History No operations and no serious illnesses other than diphtheria, mumps and tonsillitis in childhood.

Menstrual History Catamenia began at 11 years of age and was perfectly regular until 1931 when it became irregular for two months and then ceased. At about the same time she noticed that her voice was becoming harsher, that she felt irritable and clumsy and that her hair was growing coarser. She had gained about 25 pounds in weight during the previous two years. She was seen at the Lahey Clinic at that time, and was found to be overweight, nervous and florid. Her heart was moderately enlarged, no murmurs were heard, the aortic second sound was accentuated. The blood pressure was 230 mm systolic, 148 mm diastolic. Abdominal examination was negative. Pelvic examination (Dr. McCarthy) was negative. There was edema of both lower extremities. Eye grounds showed no hemorrhages or exudate, some vascular changes but no arterio-venous nicking. The blood non-protein nitrogen was 32 mg per cent, and the hemoglobin 85 per cent. Blood counts were normal, the coagulation time, 2 minutes 15 seconds. The urine showed a fixed gravity between 1.005 and 1.014. The Wassermann reaction was negative. A diagnosis of primary hypertension was made.

During the next three years the patient became increasingly fatigable, so that latterly it had been necessary for her to stay in bed very often for a day or two. The blurred vision, already mentioned, had been increasing steadily, and for three weeks before entrance had taken the form of a fixed spot before the right eye. The left eye was less affected, but reading, especially of fine print, had become difficult. The eye lids had become slightly puffy and it had become an effort to hold her eyes open. There had been some increase of the hair on the face, and her skin had been constantly discolored with "black and blue" spots. The lower legs, ankles, and feet were constantly swollen.

Physical Examination A red faced, florid, obese young woman with no deformities. The obesity is localized in the abdomen and breasts, and there are fat deposits in the axillary regions. There is pitting edema of the legs and ankles, and a number of discolored areas on the legs. There are several bluish to reddish striae on the medial aspect of each thigh, and in the axillary borders. The cheeks show a fairly rich growth of hair.

The lips are slightly cyanotic, the skin everywhere dry and scaly.

The thyroid is not palpable. The lungs are normal. Heart. The apex impulse is felt 11 cm from the midsternal line in the fifth interspace just to the left of the mid-clavicular line, the right border extends 3 cm from the mid-sternal line, the upper border is at the third rib. There are no murmurs and no arrhythmia. The blood pressure is 220 mm systolic and 160 mm diastolic. The abdomen shows marked *panniculus adiposus*, but is otherwise not remarkable. All normal reflexes are obtained, no abnormal reflexes elicited.

As preliminary diagnoses at this stage of the examination both malignant nephrosclerosis and pituitary basophilism were suggested as possibilities.

A neurological examination by Dr. Golden showed no disturbance of sensation, stereognosis and no incoordination.

Laboratory examinations. Hemoglobin 103 per cent (Sahli), red count 5,500,000, blood clotting time normal. Sedimentation rate 21 mm in one hour. Hinton, Wassermann and Kahn tests negative. Blood calcium 11 mg, cholesterol 375 mg, non-protein nitrogen 52 and 45 mg per 100 cc of blood. Glucose tolerance test. Fasting blood sugar 112 mg, 30 minutes after 100 gm glucose, 246 mg, one hour, 297 mg, three hours, 172 mg per 100 cc blood. Urine tests showed evidence of normal diluting and concentrating function, the phenolsulphonephthalein excretion was 49 per cent in two hours. Albumin varied between 0.1 per cent and 0.15 per cent on numerous examinations, and the sediment showed numerous fine granular and cellular casts, a varying number of white and red cells and on one occasion large numbers of the latter.

Pyelograms were essentially negative. Roentgenograms of the skull showed no evidence of tumor. A tuberculin test was negative. An electrocardiogram was normal except for left axis deviation. The blood pressure remained always above 200 mm systolic and 160 mm diastolic. The basal metabolism was minus 4 per cent on one occasion, and minus 8 per cent on another.

The laboratory findings made the diagnosis of malignant nephrosclerosis a very unlikely one. Pituitary basophilism remained a possibility. The masculinization, however, strongly suggested adrenal cortical tumor. It seemed advisable therefore to explore for adrenal tumor.

On May 11, 1934, Dr. Lahey operated, found and removed a "plum sized tumor" of the left adrenal. Following operation the patient's blood pressure fell to 120 mm systolic and 90 mm diastolic, and continued to fall, despite intravenous injections of saline, glucose and adrenalin. Eschatin was also administered but the patient died apparently from acute adrenal failure.

Autopsy showed removal of the left adrenal gland and extreme atrophy of the right. The latter was found with great difficulty, and weighed less than 0.5 gm. The capsule was thick, the medulla practically absent. Only a few cortical cells were vacuolated. The right ovary measured 3.5 by 1.5 by 1 cm and contained three thin walled cysts, filled with clear fluid. The left ovary was wrinkled and shrunken and measured 2 by 1.5 by 1 cm.

Microscopic examination of the removed tumor showed adenoma. The pituitary body was grossly normal, showing no increase in size. Study of serial sections by Dr. Shields Warren and Dr. Eisenhardt showed no basophilism of the anterior lobe.

Anatomical diagnosis. Marked atherosclerosis, hypertrophy of the heart, dilatation of the stomach and intestines, cholelithiasis, atelectasis of the lower lobe of the right lung, hypertrophy and degeneration of the pineal gland, surgical removal of the left adrenal body.

COMMENT

The clinical picture presented by this patient is very similar to that described by Cushing² as typical of basophilic adenoma of the anterior pitui-

tary body In fact, all the typical symptoms of that condition are present, with the possible exception of osteoporosis and kyphosis, which are not specifically noted in the record In contrast to the other two patients there was even a slight erythremia found, and the history of fatigue and exhaustion is present The one symptom which was not typical was the change in the voice, which, as has been noted, is not described by Cushing as occurring in pituitary basophilism Yet, as in the case described by Walters, Wilder et al⁴ the anterior pituitary body was grossly normal, and serial sections studied by Dr Warren and Dr Eisenhardt revealed no basophilism The discussion of the moot question of the relations between pituitary basophilism and adrenocortical tumor does not lie within the scope of this paper but it seems proper to reemphasize voice change in the female as a possibly important differentiating symptom between the two conditions

Finally, it seems worth while to call attention to the fact that in all three of the female patients reported, menstruation did not appear at the usual age In the first and third, the menarche was unusually early, suggesting prematurity, while in the second patient it was definitely late in appearing This may be pure coincidence in all three cases, but it seems worth noting in a paper which has for its purpose an addition to the records concerning a rare and little understood condition

Case 4 J K, a white 14 year old school boy, admitted to the Diagnostic Hospital, July 21, 1936, because of obesity

Family History Contained no account of obesity in any member of the family There was no family history of malignancy Four siblings are normally developed

Past History The father stated that the boy has never had any illnesses He grew and developed normally until one year before admission

Present Illness During the past year the patient had gained weight very rapidly and his facial appearance had changed markedly due to the obesity and to a dusky reddening of his cheeks On May 18, 1936, he had a sudden convulsive attack lasting from four to six hours accompanied by biting of his tongue and incontinence and followed by vomiting Following the attack he returned to his normal activities and had no more convulsions He complained occasionally of dizzy spells At the time of admission he was attending school, having no scholastic difficulties and playing normally There was no disturbance of vision, no polydipsia, no polyuria, no frequent headaches, no dyspnea nor palpitation, no digestive disturbance and no urinary disturbance The obesity and change in appearance were the factors which led his parents to bring him to the hospital

Physical Examination A 14 year old boy of unusual appearance The face is described as "full moon like" with thick fat folds below the chin and extending upward to merge with the cheeks The latter were dark, cherry red The trunk was markedly obese with prominent deposits of fat on the abdomen and on the back of the neck The arms and legs, however, contrasted sharply in size with the obesity of the trunk, neck and face The skin of the trunk and limbs was dry and slightly thickened and over the inside of the thighs showed marked marbleization Here and there on the legs were a few small bluish spots, typical of subcutaneous hemorrhage The mucous membranes were normal, musculature normal, and there was no evident deformity nor tenderness of bones with the exception of an area over the lower three ribs which was slightly tender to pressure The skull was normal in shape There was no evidence of exophthalmos The pupils were wide, circular and reacted

promptly to light and accommodation. Ocular movements were normal. There was no evidence of disturbance of the third or fifth nerves. The eye grounds, both retinae and the optic discs appeared normal. There were a few hairs on the upper lip. The mouth was normal, teeth normally developed and in good condition. Tongue, pharynx and tonsils not remarkable. Save for the fat deposits previously noted there was no abnormality of the neck. The chest was broad. The lung borders were normal to percussion and there was no abnormal dullness. The breathing was vesicular. Breasts were of feminine configuration due to the fat. The heart was normal in size, sounds not well differentiated, no murmurs. The aortic second sound was moderately accentuated. The pulse was normal in rhythm. It showed increased tension by palpation, the blood pressure was 145 mm of Hg systolic and 90 mm diastolic. The abdomen showed a marked panniculus but was otherwise not remarkable, no masses or organs were palpable. There was marked masculinity of the type of hair growth and several dark red striae were noted on both sides of the abdomen. There was considerable hair growth in the lumbar region of the back. The genitalia were markedly hypoplastic. The extremities were freely movable and showed no deformities. Reflexes were all normal with the exception of the cremasterics which were exaggerated equally on the two sides. There was no disturbance of sensation.

Laboratory Examinations The urine was normal and a test for prolan in the urine was negative. The blood showed a hemoglobin of 89 per cent, red blood cell count 5,430,000, Wassermann and Hinton tests negative. The basal metabolic rate varied in a number of observations between minus 20 per cent and minus 40 per cent. A blood sugar tolerance was performed with difficulty, the fasting blood was not obtained, but the values for one, two and three hour specimens after ingestion of 100 gm of glucose were 240 mg, 299 mg and 230 mg respectively. The corresponding specimens of urine showed glycosuria in every specimen. Roentgen-ray plates of the pelvis and skull showed no pathologic changes.

A diagnosis of pituitary basophilism was made and he was given four treatments with roentgen-ray to the pituitary region, with complete relief of the headaches and slight loss of weight. There was little other change in his condition for the next four months. He then developed a small but deep ulceration of the anterior surface of the left lower leg which healed very slowly. His blood pressures during the four months had varied between 120 and 140. The boy seemed cheerful and had no complaints. Intravenous pyelograms gave normal findings. On April 10, 1937, it was noted that his condition was unchanged, but a few days later he developed a second ulcer just below the first. This increased rapidly in size and became as large as the palm of one's hand and discharged purulent material. The boy was, therefore, readmitted to the hospital where it was noted that the red color of the face was even more dusky. The abdominal striae were more pronounced and striae had appeared in both axillae and on the left upper arm. He had regained the weight lost after the first roentgen-ray treatments. The skin of the arms and legs had become very dry and thick and varied from bright red to bluish red in color. The left ankle was edematous and motions of the foot were painful. The fat deposits previously described had definitely increased.

The fasting blood sugar on two different days was 282 mg and 245 mg per 100 c c. There was slight glycosuria. He was given insulin 25, 15 and 20 units with a reduction of sugar to normal. The omission of the insulin was not followed by an increase in the blood sugar and the boy seemed more alert. There was, however, considerable general weakness. Roentgen-rays, May 22, showed definite osteoporosis. The basal metabolism was minus 27 per cent. The glucose tolerance showed: Fasting 124 mg, thirty minutes after 100 grams of glucose, 185 mg, one hour, 249 mg, two hours, 299 mg, and three hours 230 mg. The fasting and 30 minute specimens

of urine were sugar free. The one hour specimen showed a trace of sugar, the two hour 3 per cent and the three hour specimen 32 per cent. The sedimentation of the blood was 15 mm in one hour (Westergren).

Roentgen-ray of the skull showed no evidence of tumor. The basal metabolic rate was always subnormal. Temperature, pulse and respiration were normal. Blood platelets 409,000, phosphatase 438 units.

The patient was transferred to the Massachusetts Memorial Hospital for exploration of the adrenal gland. His condition at the time was extremely poor and he failed to rally postoperatively, death occurring without further significant developments.

The chief findings at autopsy were as follows. There was a large symbiotic ulcer on the lateral aspect of the left leg. The right lung was partially collapsed and the right lower lobe contained a multilocular abscess approximately 4 cm in diameter. It contained about 5 cc of thin, granular, purulent material. The liver was pale yellowish brown, lobulations poorly defined, distinctly greasy and somewhat friable. The pancreas weighed 100 gm and showed many scattered subcapsular foci of fat necrosis varying from 3 to 10 mm in diameter. The pancreatic duct showed no evidence of obstructive inflammation or other pathologic lesion. The adrenals together weighed 15 gm and were distinctly enlarged although they showed no specific adenoma nodules. The right adrenal measured approximately 6 cm by 3 cm by 6 mm. The left adrenal was distinctly mal-formed and larger than the right. The upper portion seemed normal while the lower portion formed a well defined beaver-tail-like accessory lobe. It measured 7 cm in length, 3 cm in diameter and had an average depth of 6 mm. Serial sections showed a normal gross relationship between the medulla and cortex. No adenomatous or other tumor nodules could be seen. The cortical tissue was pale yellowish brown and showed less lipid storage than is normally observed. The genitalia were infantile. The thymus was so extremely small and atrophic that it was found with great difficulty. Only the slightest remnants suggesting thymic tissue were discovered. The thyroid was normal in size, shape and position and appeared normal on section. The pituitary was distinctly shrunken, measured approximately 1 cm in its long axis and 4 mm in its diameter. It was distinctly more dense and fibrous than normal. At its left lateral pole the cut surface presented a distinct nodule approximately 3 mm in diameter of a brighter yellow than the surrounding tissue and having no other specific characteristic. The vertebrae showed a marked osteoporosis so that in many places the dark reddish brown marrow could be seen through the outer cortical bone which could be easily incised with a scalpel.

Pathological Diagnosis Adrenal hypertrophy, adenoma of the anterior pituitary lobe, chemical pancreatitis with extensive fat necrosis, thymic atrophy, testicular atrophy, fatty degeneration of the liver, cellulitis of the neck, symbiotic ulcer of left leg, toxic lymphadenitis. The histological findings are not yet available. Assay of the liver, adrenals and testicles for estrin showed more than 500 m u in the liver extract, but was negative in the other two tissues. No follicle stimulating or luteinizing hormone could be demonstrated.

COMMENT

Clinically, this patient presented the typical picture of pituitary basophilism described by Cushing,² and the pathological findings, though not complete, furnish confirmatory evidence. Postulating a primary basophilic adenoma, the other endocrinopathies can be explained as secondary manifestations of disturbed pituitary function, while no such logical sequence can be constructed if the adrenal hypertrophy be regarded as the primary

disturbance In adrenal hypertrophy virilism, not infantilism, would be expected No significance is attached to the hormone assays they are reported as a matter of record

SUMMARY

Four cases, all presenting certain similar features suggesting the adrenal cortical syndrome, are presented In two, the diagnosis was confirmed by operation or autopsy In a third, the diagnosis seems reasonably established by operation, and in the fourth, an adenoma of the anterior pituitary lobe was found at autopsy The histories, physical and laboratory findings together with the findings at operation or autopsy are reported

My thanks are due to Drs Prather, Hazard, Lahey, Warren, Eisenhardt and Branch for their generous cooperation in furnishing surgical and pathological reports I also wish to thank all the staff members of the New England Medical Center who contributed to the diagnostic studies herein reported

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AUTO PASSIVE TRANSFER IN ALLERGY *

By D MURRAY COWIE, M D , F A C P , *Ann Arbor, Michigan*

ON May 18, 1936 Samuel W , 52 years of age, presented himself for allergic studies because of an uncontrollable asthma that had been going on for five years He had been examined elsewhere by the scratch method The reactions secured by this method had not been satisfactory, in that after carrying out the eliminations suggested by these tests no relief was experienced

On intradermal examination with standardized allergens² the patient reacted negatively to 80 out of 96 Of the 16 positive reactions only five could be considered unquestionably positive feathers, black pepper, sheep wool, mushroom and corn

There was no question concerning the allergic nature of this patient's asthma That being the case there was every reason to believe that his circulating blood was laden with allergic antibody

In the prosecution of scientific observations on clinical allergy, three prime factors must at all times be considered antigen, antibody, tissue cell The nearer we come to being able to control these factors the more trustworthy will be the interpretation of the results of experimentation At least two of these factors may be satisfactorily controlled, antigen and antibody The tissue cell is, and probably always will be, a variable and possibly an indeterminable factor

The patient Samuel W was endowed with the two essential somatic factors antibody, tissue cell Why, then, did his skin not react to specific antigen Such instances are not uncommon Specific sensitivity in such individuals is proved by the well known Prausnitz-Kustner phenomenon, brought about by the passive transfer of the allergic person's serum into the skin of a non-specifically allergic person, where, after a certain latent period, it locally passively sensitizes the skin, and when the third factor, specific antigen (allergen) is injected into it a characteristic intradermal allergic reaction develops The Prausnitz-Kustner phenomenon was demonstrated by use of the patient's (Samuel W) serum

To return to the question, why did the patient's skin not react to the injection of the specific antigen, to which we had now proved he was sensitive? What difference could there be in his skin to that of a recipient's which had been proved to be non-specifically allergic but could be made passively so by the introduction of allergic serum from another person? May there be, in such instances, some unusual variation in the quantitative rela-

* Received for publication August 12, 1937

tions of the circulating antibody? May there be something defective in the skin mechanism? Had something occurred to make the patient's skin less sensitive than it may have been at some other time?

I *To test the first hypothesis* it was a simple matter to inject the patient's skin with his own antibody laden blood serum. If his skin cells were capable of being passively sensitized a reaction should occur when specific antigen is injected into the treated area because, to any antibody already circulating through the skin, there would be added concentrated antibody. When this experiment was carried out a typical intradermal allergic reaction occurred. I have designated this phenomenon as *auto passive transfer*¹ because the patient's own passively sensitizing blood serum is transferred into his own skin, where it sojourns for a certain time, then disappears. This is suggestive, but not positive, evidence that the failure of the skin to react, in the untreated areas, is due to insufficient antibody coming to it.

METHOD

The allergens (antigens) used were standardized² in my laboratory by Dr. John J. Engelfried to an exact nitrogen content of 5 mg. per cent, the same batch of allergen being used for comparative observations. Exactly 0.03 c.c. is injected intradermally as the test dose. This is done very carefully, infiltrating the skin slowly so as not to induce a traumatic reaction.

The Syringe and Needle. New B. D. Tuberculin Syringes and No. 26 (27 better) gauge rustless needles are used. After use they are carefully rinsed in warm distilled water. The needle is removed and the collar carefully cleaned with a cotton applicator and the syringe again thoroughly rinsed in distilled water. After this suction is applied by a Chapman pump which aspirates distilled water through the barrel. Alcohol (96 per cent) is then rinsed through syringe and needle to remove all traces of water. The plunger and barrel are separated and allowed to dry in the air. The needles are blown out with dry air and after checking the points, are put singly into small glass tubes between plugs of cotton to be sterilized. The syringe plunger and barrel (apart) are wrapped in heavy wrapping paper. The needles and the syringes are sterilized by placing them in an oven at room temperature, raising the temperature to 220° C., cooling to 100° C., again raising to 220° C. and allowing to cool. The needles are checked with a magnifying glass and specially sharpened, by the Department of Engineering, after they have been used approximately 10 times.

All this is done to destroy traces of allergen left in the syringe and needle, and to avoid the presence of moisture that would dilute the allergen. In other words the glassware and needles used in this investigation were chemically as well as bacteriologically sterile. Formerly our syringes and needles were rinsed in dichromate cleaning solution. This was hard on the needles. We have returned to this practice, plus the above details, as the rustless needles now used withstand this action fairly well.

Serum Transfer. A precise amount, 0.05 c.c., of the patient's serum is injected intradermally into as many skin sites as are desired. In our present routine of *auto passive transfer examination*, 32 transfers are made on alternating days. The sites or areas of transfer are tested for specific sensitivity, after 24 hours, by the intradermal injection of the standard amount of allergens (0.03 c.c.). In quite a percentage of passive transfers there is an immediate reaction following the injection of serum that cannot be differentiated from a positive allergen intradermal reaction. It disappears in the ordinary time. Its nature is considered in another paper.

Recording the Reactions The reactions are measured in millimeters, with fine pointed dividers, in two opposite or perpendicular diameters. The average of the two readings is charted. The wheal and the area are both recorded on the working sheet. The area measurement of course includes the diameter of the wheal. The character of the wheal with regard to the number of pseudopods and the degree of edema is also recorded as well as the color of the area and its degree.

W = Wheal E + and E = marked or slight edema

P 1, 2, 3, or 4 = the number of pseudopods

A = Area The number gives the average diameter from which the area surface may be computed ($a = \pi r^2$)

R = red, R + very red, R — less red

F = faint, F = very faint, F = very very faint

M = Mottled

Thus the following record, Ragweed $W 12 P_2$ means a wheal of 12 millimeters average diameter with two pseudopods and a red area 31 millimeters average diameter or, as in the following tables only the average diameters of the entire reaction at the time specified are recorded as 35 R +, 36 R —, 30 F. These are the 15 minutes, 30 minutes and one hour readings. Some reactions are, for the greater part, mottled, (M), particularly about the periphery. Measurements of these are made with the dividers to the edge of unquestioned color. Observations are all made at exact time intervals announced by a mechanical timer. Seldom were measurements made excepting by myself, to assure no interference by the personal equation.

TABLE I

Auto Passive Transfer Examination

S W, Age 52, Bronchial Asthma

May 18, 1936

Allergen	Intradermal Test in		Allergen	Intradermal Test in	
	Untreated Skin Area mm	Auto Passive Transfer Area mm		Untreated Skin Area* mm	Auto Passive Transfer Area mm
Sweet Potato	0	28 R	Lemon	0	0
Cotton Seed	0	27 R	Navy Bean	0	0
Cucumber	0	27	English Walnut	0	0
Spinach	0	23 F	Coffee	0	0
Pineapple	0	21 R	Pear	0	0
Cocoa	0	21 R	Beef	0	0
Grapefruit	0	17 R	Milk	0	0
Orris Root	0	16 R	Lima Bean	0	0
Vanilla	0	0	Cauliflower	0	0
Oat	0	0	Lamb	0	0
Cherry	0	0	Apple	0	0
Cocoanut	0	0	Rye	0	0
Silk	0	0			

* Control area on opposite side

OBSERVATIONS

A few illustrative observations on *auto passive transfer* are recorded in the accompanying tables which are self explanatory.

Case 1 The first case is that of Samuel W, 52 years old, referred to in the opening paragraph. I made 17 transfers of the patient's serum into the skin of his back on June 24, 1936, 8 on July 3, and 16 on July 13, a total of forty-one. The following days the same number of standard food allergens² was injected intradermally into these transfer sites. These allergens were selected from a list of those to which the patient had failed to react on the regular intradermal examination. There resulted eight unquestioned positive reactions. These are arranged in table 1 in the order of the degree of reaction together with 14 of the negative reactions. Accordingly eight additional offenders were found by this method of examination, one of which, cucumber, was of undoubted clinical significance. The negatively reacting allergens serve as a good control.

Case 2 Mrs Dora R, 38 years old, suffering with severe asthma, was given 96 intradermal tests in our Sensitization Clinic. No relief was secured from putting into effect the eliminations indicated by this examination. I had her sent to my laboratory where I made 11 auto passive transfers into the skin of her back (November 17, 1936). The following day these sites were tested by the intradermal injection of 11 allergens she had failed to react to. Eight of these were found to be positive (table 2).

TABLE II
Auto Passive Transfer Examination

Mrs Dora R, Age 38, Asthma

November 17, 1936

Allergen	Intradermal Test in		Allergen	Intradermal Test in	
	Untreated Skin mm	Auto Passive Transfer Site mm		Untreated Skin mm	Auto Passive Transfer Site mm
Lemon	0	29 R	Silk	0	17 R
Wheat Leucosin	0	21 R	Grape	0	16 E
Wheat Glutenin	0	19 R	Beef	0	0
Rice	0	19 F	Cheese	0	0
Wheat Globulin	0	17 F	Lactalbumin	0	0
Wheat Proteose	0	17 R			

Case 3 Mr G V, 65 years old, who showed multiple sensitization in 1934, returned for reexamination in February 1937. The putting into effect of eliminations suggested by his first examination had brought relief from his cutaneous symptoms. I made 96 intradermal tests and found him sensitive to nine. To test the effect of auto passive transfer I made nine transfers of his serum into the skin of his arms (February 22, 1937) and tested these sites the following day to nine food allergens, to eight of which he had given negative reactions on my last intradermal examination but to which he had given positive reactions in 1934. He gave definitely positive reactions to three of these (table 3).

Case 4 Willard O, 12 years old, was referred from the Otolaryngology Clinic for allergic studies because of allergic rhinitis. In 1936 he was given 32 intradermal tests and reacted to two allergens, wheat leucosin and pineapple. In February 1937 he reacted to the same two plus feathers. On March 1 we made 40 auto passive transfers into the skin of his back and tested these sites the following day by the intradermal injection of allergens he had failed to react to. He reacted to 12 of these as shown in table 4.

TABLE III

Auto Passive Transfer Examination

G V, 65 years old

February 22, 1937

No	Allergen	Intradermal Test in		
		Untreated Skin 1937	Auto Passive Transfer Site 1937	Untreated Skin 1934
1	Wheat Proteose	0	33 R	28 R
2	Sweet Potato	0	21 R	20 R
3	Feathers	0	15 R	22 R
4	Sheep Wool	0	14 F	20 F
5	Ginger	0	0	32 R
6	String Beans	0	0	28 R
7	Banana	0	0	25 F
8	Yeast	0	0	28 R
9	Ragweed	0	0	0

TABLE IV

Auto Passive Transfer Examination

Willard O, Age 12, Allergic Rhinitis

March 1, 1937

Allergen	Intradermal Test in		
	1936	1937	Auto Passive Transfer Area 1937
Lactalbumin	0	0	26 R
Evap Milk	0	0	20 R
Apricot	0	0	15 R
Banana	0	0	16 R
Lemon	0	0	18 R
Orange	0	0	20 R
Sheep Wool	15	0	32 R
Cocoa	0	0	19 R
Potato	0	0	21 R
Lettuce	15	0	15 R
Cotton Seed	14	0	16 F
Peach	0	0	21 R

12-2-36

3-20-37

Case 5 Mrs Cassie M, 51 years old, a case of asthma, was referred from Dr Sheldon's Allergy Clinic for auto passive transfer studies, May 21, 1937 This patient had been given 172 intradermal tests in August 1936 and had reacted positively to 85 She returned for reexamination in May 1937 because of a continuance of her asthma Tests for the pollens and some molds were given Only slightly positive reactions to four were obtained Oat grass +, rye grass +, poplar ± and June grass ± Because of the faint reactions these tests were repeated with the same result Table 5 records the comparative intradermal and ophthalmic tests and those of the auto passive transfer areas Unfortunately rye grass and poplar allergens were not included By reference to table 5 it will be seen that she gave definite reactions to nine allergens, including two she had reacted to, slightly, before

TABLE V

Mrs Cassie M , Age 51, Asthma

May 21, 1937

Allergen	Test 5-18-37 mm	Auto Passive Transfer Exam 5-21-37 mm	Allergen	Intradermal Test 5-18-37	Auto Passive Transfer 5-21-37
Ragweed	0	0	Maple	0	33 R
Timothy	0	29 R	Alternaria	0	0
June Grass	±	27 R	<i>Aspergillus fumigatus</i>	0	28 R
Oat Grass	+	27 R	<i>Aspergillus niger</i>		24 R
Elm	0	36 R	<i>Trichophyton interdigitale</i>		0
Blue Grass		30 R			
Dandelion		32 R			

It was our understanding when this patient was sent to us that she had failed to react to the entire list of 172 allergens with the exception of those mentioned above, accordingly we had prepared her skin the day previous for 47 auto passive transfer tests. There were therefore 35 sites left, these we tested with food allergens. It is of interest to record the results (table 6), even though we do not have an intradermal control, because of the many unusually marked reactions obtained, and to illustrate for comparison how the skin may react under these conditions. I am also recording in this table the results of tests done ten months previously with the same allergens. The notation, however, is different. It is based on the appearance of the wheal without reference to the area. A wheal of about 5 mm in diameter is recorded ±, 8 mm +, 10 mm ++, 13 mm +++, 13 mm or larger with pseudopods ++++. It is our custom to measure both wheal and area and to record a wheal of 8 mm without appreciable area as negative. A wheal of 10 mm as ±.

Case 6 Mrs Irene R, aged 36, a case of asthma, was referred to me from the Clinic of Internal Medicine for auto passive transfer examination because she failed to react to any of the pollens. We made 39 auto passive transfers to the skin of her back and the following day injected seven pollen allergens and 32 food allergens. All the tests were negative.

Case 7 Robert S, 4 years old, a case of asthma, was tested with 96 antigens intradermally on March 1, 1937. He reacted to feathers only (19 mm). On March 18, I made 16 auto passive transfers and tested the areas the following day with 16 food allergens. He reacted positively to two of these, orange, 15 mm, and potato 17 mm. The entire examination had been quite a trial to this rather nervous little chap and tears constrained me to proceed no further.

Comment These observations, I believe, prove beyond question that an allergic person's skin which fails to react to specific allergen can be passively sensitized with his own serum, and they suggest that the inactive skin is made to react by bringing more specific antibody to it. This demonstration that an allergic person's inactive, or refractory, skin can be passively sensitized with his own serum and made to react to specific allergen, suggests that the skin inactivity may be due to a quantitative defect of circulating antibody, or to some inability of the skin cells to take up antibody as it circulates through it. However, it is of further interest to know whether an allergic person's skin that *does react* to the injection of specific allergen may be made to react more vigorously by this mechanical introduction of

more and concentrated specific antibody into it. The reactions assembled in table 7 seem to show that such more vigorous reactions may be thus induced, and add evidence that quantitative antibody influences may be responsible for failure of an allergic person's skin to react. There is, however, an instance where just the opposite result occurs, No 8. More observations are necessary before this point can be considered definitely settled.

TABLE VI

Mrs. Cassie M., 51, Asthma Continued (See text)

Allergen	Intradermal Test 8-11-36 mm	Auto Passive Transfer 5-21-37 mm	Allergen	Intradermal Test 8-11-36 mm	Auto Passive Transfer 5-21-37 mm
House Dust	0	W 17 A 35 R	Wheat Leucosin	++	W 16 35 R
Beef	0	15	Wheat Proteose	+++	22 R
Cheese	0	0	Apple	0	W 17 31 R
Chicken	0	0	Apricot	++	20 F
Egg White	0	0	Banana	0	W 18 28 R
Egg Yolk	0	0	Grape	0	22 R
Lamb	0	0	Grapefruit	++	W 23 P2 40 R
Cow's Milk	0	22 R	Lemon	+++	40 R
Casein	0	0	Orange	+	W 30 P2 44 R
Lactalbumin	0	16 F	Peach		29 R
Kapok	++++	28 R	Pear	+++	W 21 P2 32 R
Pork	0	0	Pineapple	+	W 20 32 R
Barley	0	25 R	Fig	+++	W 21 24 R
Oat	0	W 18 23 R	Evap. Milk	0	14 F
Rice	0	24 R	Rye	0	19 R
Wheat Gliadin	0	0	NaCl Nipagen*		
Wheat			Control		0
Glutenin	0	0			
Wheat Globulin	+	22 R			

* Preservative 7

This same phenomenon, described in connection with auto passive transfer, may also be induced through passive transfer. That is a positive intradermal reaction may be enhanced by the introduction of more specific antibody from another person into the skin. This is shown in table 8.

May there be something defective in the skin mechanism? My observations on the Prausnitz-Kustner phenomenon seem to demonstrate clearly that there is something in the skin mechanism itself that may be responsible for the degree of the skin reaction. It is easy to demonstrate that the skin

TABLE VII

Showing Instances of the Enhancing Effect of Auto Passive Transfer on the Skin Reaction

No	Patient	Allergen	Intradermal Reaction in	
			Untreated Skin mm	Treated Skin* mm
1	S W	Corn	19	26 R
2		Mushroom	19	20 R
3		Feathers	31	46 R
4		Sweet Potato	13	28 R
5		Orris Root	13	16 R
6		Cocoa	13	22 R—
7	Mr G V Willard O	Black Pepper	25	30 R
8		Sheep Wool	31	17 R
9		Wheat Proteose	28	33 R
10		Wheat Leucosin	24	30 R
11		Feathers	18	28 R
12		Sheep Wool	15	32 R

* Area of passive transfer

TABLE VIII

Allergen	Intradermal Test on Untreated Area mm	Intradermal Test on Passive Transfer Area mm
Sweet Potato	13 F	43 R
Salmon	13 R	38 R
Mushroom	19 R	38 R
Feathers	25 R	51 R
Spinach	19 R	25 R
Sheep Wool	13 F	25 R

of different skin donors, or recipients, for passive transfer may vary greatly in its ability to react to allergen^{3 4} For example, I record in table 9 two instances where the skin was negative to the intradermal test before passive transfer was done After passive transfer, one reacts more vigorously than the other or does not react at all, yet exactly the same amount of antibody and the same latent period elapsed in each case before the testing was done It is also shown in table 9 that reactions in auto passive transfer areas are as likely to occur as they are in passive transfer areas Donor H's skin reacted oftener and more vigorously than did donor E's, and auto passive transfer areas reacted as frequently and as vigorously as the passive transfer areas of donor E

Had something occurred to make the patient's skin less sensitive than it may have been at some other time? Reference to tables 3 and 4 furnishes illustrations of a skin, which was active a year or several months before, losing its ability to react and being made to react by means of auto passive transfer

TABLE IX

Different Reaction Ability of Different Skin Donors to Allergen on Passive Transfer

Allergen	Intradermal Test on Skin Donor H	Intradermal Test on Skin Donor E mm	Passive Transfer Test on Skin Donor H mm	Passive Transfer Test on Skin Donor E	Auto Passive Transfer
Silk	0	0	51	0	0
Cotton Seed	0	0	31	19	27
Date	0	0	31	20	13
Salmon	0	0	38	0	28
Vanilla	0	0	25	0	0
Cherry	0	0	19	0	0

These observations seem to indicate that failure of an allergic person's skin to react may be due to one or a combination of two things—quantitative antibody influences, some change in the skin mechanism whereby specific antibody is not properly brought to it or is kept away from it

Determination of the quantity of circulating passively sensitizing antibody To carry this work further some method for quantitating or titrating circulating sensitizing antibody must be worked out, investigated and found to be satisfactory

By using known amounts of specific antigen (allergen) the amount of antibody in a given serum may be determined by an absorption experiment It has been shown in this laboratory and elsewhere ^{3, 4, 5, 6} that specific antigen

TABLE X

Sensitizing Antibody Titer

Robert M, 11 years Short Ragweed

No	Antibody + Antigen			Reaction in Passive Transfer Area mm
	Serum cc	NaCl cc	Antigen mg % prot	
1	0 35	0 15	20	0
2	0 35	0 15	10	0
3	0 35	0 15	5	0
4	0 35	0 15	2 5	26 R
5	0 35	0 15	1	43 R
6	0 35	0 15	0	43 R+

- 1 Original antigen extract 0 666 mg per cc in sterile 0 85% NaCl solution 0 15 cc of this solution + 0 35 cc of serum = 20 mg % of antigen
- 2 1 cc No 1 + 1 cc of sterile 0 85% NaCl solution 0 15 cc of this solution + 0 35 cc serum = 10 mg % of antigen
- 3 1 cc of No 2 + 1 cc sterile 0 85% NaCl solution 0 15 cc of this solution + 0 35 cc serum = 5 mg %
- 4 1 cc of No 3 + 1 cc sterile 0 85% NaCl solution 0 15 cc of this solution + 0 35 cc serum = 2 5 mg %
- 5 0 8 cc of No 4 + 1 2 cc sterile 0 85% NaCl solution 0 15 cc of this solution + 0 35 cc serum = 1 mg %

destroys or renders inactive sensitizing antibody Varying amounts of specific allergen (antigen), short ragweed for example, are mixed with a given amount of the serum to be tested The mixtures are made isotonic with 0.85 per cent sodium chloride, incubated at 37.5° C for one hour without preservative, and 0.05 c c of each dilution is transferred to a recipient's skin as previously described In table 10 the strengths of the ragweed antigen added to the 0.35 c c of serum are indicated by their content respectively of 20, 10, 5, 2.5, and 1 milligram per cent protein In this instance 5 mg per cent (0.025 mg) of short ragweed protein completely neutralizes all the antibody contained in 0.35 c c of the patient's serum Antigen of the strength 2.5 mg per cent does not The actual amount necessary is therefore somewhere between these figures Table 11 shows the same thing

TABLE XI
Sensitizing Antibody Titer

M. M., 32 years Short Ragweed

2-23-37

No	Antibody + Antigen			Reaction in Passive Transfer Area mm
	Serum c c	NaCl c c	Antigen mg % prot	
1	0.7	0.3	10	0
2	0.7	0.3	5	0
3	0.7	0.3	2.5	42 F
4	0.7	0.3	1	37 R
5	0.7	0.3	0	42 R

Walzer and Bowman⁶ found that the admixture of equal parts of "the strongest pollen solution available (0.4 mg N per c c)" with a hay fever patient's serum, completely neutralized the antibody only after several hours incubation Coca and Grove⁵ were unable to quantitate the reagin present in a given serum by the serum dilution passive transfer method If in carrying out a comparative observation the same donor's skin can be used, and too much time has not elapsed between determinations, an idea of any change in the quantity of circulating antibody that has occurred during that time may be obtained Change to another skin donor is not permissible because of the variability in the reactivity of different skins Table 12 illustrates this point Ten milligrams did not neutralize all the antibody according to J. D.'s skin, but between 3 and 5 mg neutralized it according to D.'s skin and somewhere between 5 and 10 mg according to B.'s skin This again illustrates that the human tissue cell is a variable factor

The sensitivity of the skin of an allergic person varies from time to time Especially is this true of food allergy, depending as it does on the inclusion or omission of the specific food from the diet Accordingly in carrying out quantitative observations by means of the Prausnitz-Kustner

TABLE XII

Sensitizing Antibody Titer

M M, 32 years Short Ragweed

No	Antibody + Antigen			Reaction in Passive Transfer Area		
	Serum c c	NaCl c c	Antigen mg % prot	Skin Donor B mm	Skin Donor D mm	Skin Donor J D mm
1	0.7	0.3	10	0	0	14 F
2	0.7	0.3	5	33 R	0	20 R
3	0.7	0.3	2.5	38 R	42 F	23 R
4	0.7	0.3	1	38 R	37 R	23 E
5	0.7	0.3	0	48 R	42 R	35 R

Showing that the human tissue cell is a variable factor

passive transfer or the *auto passive transfer* method, there are many things that must be carefully taken into consideration, otherwise information based on the results may be fallacious

SUMMARY AND CONCLUSIONS

1 Evidence is produced to show that the skin of an allergic child or adult which fails to react to the intradermal injection of allergens to which he is sensitive may be made to react by the passive transfer of his own blood serum into his own skin

2 I have designated this phenomenon as auto passive transfer because the patient's own passively sensitizing serum is transferred into his own skin where it sojourns for a certain length of time, then disappears

3 The method of procedure is described and a few illustrative cases presented

4 These observations seem to show that the failure of an allergic person's skin to react to specific allergen is dependent upon one, or the combination of two factors, something at variance with the quantitative nature of the circulating antibody, something at variance with the skin mechanism whereby specific sensitizing antibody is not properly brought to it or is kept away from it

5 In some instances, at least, reactions to specific allergen occur as frequently and as vigorously in auto passive transfer areas as in passive transfer areas. Usually, however, passive transfer areas give the larger reactions. It seems that reactions are as likely to occur in auto passive transfer as in passive transfer areas

6 Positive intradermal reactions are very often enhanced by auto passive transfer

7 Auto passive transfer may be used as a practical method of examination when passive transfer is indicated. It overcomes the necessity for a

control intradermal examination of the skin donor, or recipient. This shortens the examination period 50 per cent, on the other hand it inflicts more tests on the patient.

8 The *auto passive transfer* method cannot, and is not intended to, replace the Prausnitz-Kustner method. It is an interesting phenomenon and I believe it opens up a new approach to the study of the fundamental principles of skin allergy. If future observations confirm those here recorded, difficulty in securing a satisfactory skin donor for passive transfer will be avoided.

9 The difficulties of quantitative estimation of allergic antibody are considered, and a method presented.

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SOME PHYSICAL PHENOMENA ASSOCIATED WITH THE ANXIETY STATES AND THEIR RELATION TO HYPER- VENTILATION *

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DURING the past several years the world, in general, has been undergoing critical social, moral, and economic changes, and, in the present state of upheaval, an ever-increasing number of patients are observed who present a symptom-complex which is intimately associated with the individual's struggle for security, for independence, or for whatever state is presumed to assure the spiritual and material happiness of the individual. This symptom-complex is essentially a representation of the interaction between emotional and physiological factors. While not seen exclusively among persons suffering from psychoneuroses, this symptom-complex is frequently found in such persons, and its manifestations are designated as anxiety states. Patients presenting the well-known pattern of symptoms haunt the offices of physicians and specialists in every field of medical practice. They are often shunted from one physician to another, and the sins of commission inflicted upon them fill many black pages in our book of achievement.

Our present interest in this problem arose from the study of a group of patients who in addition to their anxious tensional states were suffering from so-called "convulsive seizures." We observed that they presented symptoms and signs of tetany associated with hyperventilation. During this investigation it became apparent that there are also a large number of patients (variously estimated as one-fourth to one-third of the patients seen in general practice) who have, as localized manifestations of the same mechanism, a variety of symptoms referable to many structures in the body, and in whom hyperventilation precipitates and maintains a state of hyperirritability approaching clinical tetany. The symptoms may be so well localized in some cases that local disease is suspected without discovery of universal functional disturbance.

In order to make clear the manner in which psychological disturbance alone can produce symptoms of tetany, the well known causes of tetany will first be reviewed briefly.

The symptom known as tetany is usually defined as a painful, tonic

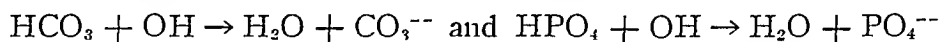
* Presented in brief at a clinic on the same subject, given at the Philadelphia meeting of the American College of Physicians on May 1, 1935.

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spasm of the muscles of the extremities. Many studies have been made in an effort to explain the manifestations which occur in the better known types of tetany. In general, tetany is thought to depend (1) on the degree of mobilization of the calcium ion, probably the diffusible fraction, (2) on the presence of alkalosis, or (3) on the existence of tissue anoxemia.

In hypoparathyroidism, there is a reduction of the serum calcium, an increase in the carbon dioxide combining-power, and an increase in the serum phosphorus. When a state of hypocalcemia and alkalosis is present, the degree of tetany depends upon the threshold of the particular patient to the stimulus he receives.^{1 to 4}

In gastric tetany, alkalosis results from loss of hydrochloric acid from the stomach,^{5, 6} and increase in the carbon dioxide combining-power of the blood⁷ because the following reaction takes place



It is suggested that in this disturbance in the chemical state of the blood, the diffusible calcium becomes fixed, and that the spasms which occur are really the result of alkalosis and hypocalcemia.^{3, 5} Definite proof of this statement is lacking, however, and alkalosis alone may be the cause of the symptom.

In infants suffering from tetany, reduction of the serum calcium follows an increase in carbon dioxide combining-power. There is one major difference, however, i.e. that the serum phosphorus rarely deviates from the normal.^{1, 8}

The so-called "bicarbonate tetany" can be induced in adults without the reduction of the calcium ion if a large enough quantity of sodium bicarbonate is ingested. If the H-ion concentration is reduced to 10^{-6} or less, tetany will occur. Although there is some disagreement,⁹ it is stated¹ that the ingestion of any anion which will combine with calcium to produce an insoluble salt, will cause tetany. Included among these anions are carbonate, phosphate, citrate, oxalate, and fluoride. It is known that in normal individuals the production of tetany by the ingestion of phosphates can be accomplished only by the use of large amounts of the salt, whether it be acid, alkali, or neutral salt. In such circumstances,¹⁰ the phosphates and the sodium ion concentration are increased, and the calcium and magnesium ions are decreased.

In rickets, during the healing stage, a form of phosphate-tetany occurs. In this state the interrelation of the calcium and phosphates is more labile, and the ingestion of normal amounts of phosphates is enough to depress the serum calcium and cause the spasm to take place.¹

In discussing hyperventilation tetany, it is important to understand the physiological background which makes this symptom-complex more evident in anxious individuals than in others with more stable emotional control.

That the state of hyperventilation and its subsequent effects are not a

discovery of the present century, is well illustrated by the passage quoted below which was suggested to us by Dr Sanford Larkey

Melancholoke folke are commonly giuen to sigh, because the minde being possessed with great varietie and store of foolish apparitions, doth not remember or suffer the partie to be at leisure to breathe according to the necessitie of nature, whereupon she is constrained at once to sup vp as much ayre, as otherwise would srue for two or three time, and this great draught of breath is called by name sighing, which as it were a reduplicating of the ordinary manner of breathing In this order it falleth out with louers, and all those which are very busily occupied in some deep contemplation Sillie fooles likewise which fall into wonder at the sight of any beautifull and goodly picture, are constrained to giue a great sigh, their will (which is the efficient cause of breathing) being altogether distracted, and wholly possessed with the sight of the image

—DuLaurens, Andre

A Discovrse of the Preservation of the Sight, of
Melancholoke diseases, of Rheumes, and of old
age London 1559 Verso, o3s

It will also be remembered that Shakespeare, in his *Seven Ages of Man*, in "As You Like It," refers to "lovers sighing like a furnace"

With these reminders that much of that which is to be discussed was described long ago, it is our purpose to re-word these phrases and apply new interpretations which will clarify the understanding of a problem that has been heretofore avoided or regarded superficially Likewise, it is hoped that the plan of study and of treatment which is to be described will be used as an aid to the solution of such problems in the future

A radical departure is made by those who believe that a physical syndrome can be provoked by an emotional state such as anxiety In the past, most physicians have consciously or unconsciously, felt that such symptoms were manifestations of an overactive imagination, or, more likely, that they represented an attempt on the part of the patient to gain the center of attention of his family, friends or physician However, there is no doubt that these patients with anxiety do suffer actual symptoms such as pain, as the result of changes in function or even in structure which have taken place because, and only because, of the preexisting anxiety This latter thesis will doubtless be met with considerable opposition from many internists and psychiatrists It is our opinion that emotional conflicts which are permitted to continue for a considerable length of time predispose the individual to structural disease It is presumed, therefore, that a chronic state of anxiety induced by such a conflict is of greater importance than is generally believed, and that its eradication, or more properly its resolution, is of utmost importance in preventing future structural, or so-called "organic," disturbances The philosophical implications of this concept are consistent with modern knowledge of many symptom-complexes in medicine

In offering an explanation of the interaction of anxiety states and the physical syndrome, we shall present the histories of a series of patients to

illustrate various combinations of the phenomena which have been erroneously interpreted as syndromes of organic disease that they resemble

Symptoms, regardless of whether they are of somatic or psychic origin, are manifestations of disturbance of function. Although disorders of the psyche are known to occur without any recognizable effects on the soma, it should be made clear that no attempt will be made to divorce them. Disorders of the psyche represent disturbed functions of the total personality. Further, prolonged influence of disturbances in function in certain parts of the brain, notably the hypothalamus and basal nuclei, induces functional changes throughout the body which, if continued, may lead to local peripheral structural changes. In turn, these peripheral alterations in function and structure promote further psychical reactions which tend to aggravate the total process. Thus syndromes now well recognized are established, and the true basic nature of the malady as a primary disturbance in function is erroneously classified as being of organic or structural origin.

The concept which has been described is the outgrowth of the study of patients in whom the symptoms of grand mal, of angina pectoris, of peptic ulcer, of constriction of the sphincters of the esophagus, bladder and other hollow organs, and of Menière's syndrome, were found to be psychogenic and not primarily on local or structural bases. These patients were observed to respond to therapy directed toward decreasing nervous irritability by the use of medicaments and diet intended to diminish tissue alkalosis and tissue anoxemia. Later their symptoms were further alleviated by more prolonged methods of psychotherapy.

In the group of patients reported, the organic diseases suggested by their symptoms were ruled out by the usual diagnostic procedures, so that each was known to suffer from a "pseudo-disease" the symptoms of which, in all cases, were the result of the same cause—*anxiety*. It is believed that in the convulsive state there exists a generalized nervous phenomenon, of nervous origin, with explosive stimulation of the patient's muscular system. In the other disturbances a similar but more localized reaction occurs. It is an hypothesis that these various syndromes are the result of an increase of central (nervous) and general (humeral) irritability which, in some instances, leads to tetanoid contractions or to spasms in a specific locality that, in all probability, are initiated by tension and nervous strain subsequent to *anxiety*. It is really made possible by a physical and a chemical disturbance resulting in a localized tissue alkalosis, a tissue anoxemia, or a tissue *hydremia*.

Viewing these symptoms as manifestations of tetanoid contractions, or of peripheral nerve stimulation, or of both, diagnostic studies were undertaken which showed that this type of tetany differs from the recognized types of tetany, and is not associated with disturbances in calcium metabolism. Rather, it depends upon the other electrolytes and their relation to the acid-base balance ^{2, 5, 11, 12, 13}

THE EXAMINATION OF THE PATIENT

Among the tests performed, an exercise in hyperventilation¹² is included for several reasons. It is well to establish the diagnosis in this manner because repetition of the symptoms emphasizes to the patient the value of control of respiration. Likewise, he is relieved to discover that his symptoms are not those of organic disease, for it is demonstrated that he can produce them at will. Often the patient is so impressed and comes to have such faith in the physician's ability that contact or "rapport" is easily established, making psychotherapy more effective. The method is of value because studies of the alkaline shift in these patients can be made, and the efficacy of the various forms of treatment can be compared from time to time. In some instances, when the exercise is again given at a later date, it is observed that the induction-time, or period from beginning of the exercise to the appearance of the first symptoms, has increased, and that the intensity of the reaction has diminished. It is understood that normal persons will show the same symptoms if hyperventilation is continued long enough. The point of importance is the ease with which these patients are thrown into a state of tetany because they are on the threshold of attacks periodically or constantly.

The procedure is comparatively simple. Following a routinely complete history and physical (including neurological) examination, to exclude well-recognized disease, the following observations are repeated before and after performing the exercise: pulse rate, blood pressure, and reflexes, including Chvostek's and Hoffman's signs. Samples of urine are taken. The patient, then lying in a comfortable position without the inhibition of constricting clothing, is asked to breathe with the regulation of the hand of the examiner placed over the epigastrium. The lightest possible pressure is made, and the rhythm is initiated so that respirations occur at the rate of 18 to 20 per minute. The time-interval from the beginning of the test to the onset of symptoms is noted. Effort is made to induce a state of carpopedal spasm,¹² or a repetition of the symptoms of the chief complaint. If no reaction is obtained within 30 minutes, the procedure is discontinued. One should judge whether or not the patient is at ease. Some patients become slightly excited and do not breathe regularly, and the slight pause they unconsciously insert into the cycle is enough to maintain the normal acid-base balance. After the results are obtained, the patients are given carbon dioxide and oxygen inhalations (30 per cent CO₂ to 70 per cent O) to relieve the spasms or other symptoms. (Having the patient hold his breath or re-breathe into a paper bag may likewise clear off the symptoms promptly.) While this improvement is being accomplished, with the patient breathing at the same rate as before, the procedure is explained to the patient in non-technical language. Simple comparisons are made to demonstrate to him the mechanism involved, and conclusions are drawn illustrating to him his rôle in the production of his own symptoms, and to show how easily and

simply he may regain his former feeling of well-being. Should the patient not cooperate well, calcium chloride, 5 c c of a 10 per cent solution, may be given intravenously, and the reactions may be explained later when the patient is more quiet.

PROTOCOLS OF EXAMPLES OF SEVERAL TYPES OF THE ANXIETY STATES

Below are the histories of a group of patients, illustrating the various types of responses which follow the common prodromal symptoms. Typically, all of these patients give a story of an encounter with some difficulty which causes emotional stress and anxiety. There is palpitation and tachycardia, hyperpnea, and a feeling of great weakness and fatigue. Within a variable period, there follow paresthesias of the hands and feet, and isolated muscular contractions which are associated with pain or tension similar to the symptoms mentioned in the patient's chief complaint. The characteristic local responses of which the patient complains are repeated quite regularly in successive attacks.

GROUP I

Tetany

Case 1 D E, female, aged 24, separated (Case 6, Chart 1)

Chief complaint Spasms of the hands and feet, duration one month

Present illness Two years before entry the patient had experienced numbness in both hands, which had responded to intravenous iron medication. Six months prior to entry, while sitting in a theater, she found that she was unable to swallow because of stiffness of her throat muscles. Two months before entry she had severe headaches for which she again received intravenous iron therapy. At this time she started proceedings for a divorce. Shortly after, she experienced gaseous distention and diarrhea. She became worse following alkalinization. One month prior to entry, while in her lawyer's office she noticed numbness of her hands and feet and a "puckering" sensation about her mouth. Later she had stiffness of the muscles of her hands and feet. Subsequent attacks progressed to the typical carpopedal spasm of tetany. Paresthesia of the skin of the chest-wall was noted. The patient stated that carbonated water alleviated these attacks.

Past history contributed nothing

Family history Her father, aged 49, and mother, aged 48, were living and well. They had been separated for years.

Marital history The patient had been married for four years. Her husband drank considerably. There had been recent separation, and divorce had been obtained.

Physical examination All findings were negative or within normal limits. The only pertinent observation was that the patient talked very hurriedly and took many deep breaths.

Neurologically, perception by senses was normal throughout. Muscles were equal and active in all movements. Reflexes were not hyperactive and were equal.

Laboratory tests Urine, stool and blood were within normal limits. Gastric analysis, absence of free HCl, but normal response to alcohol meal. Blood calcium, total 8.67 mg per cent, diffusible 4.62 mg per cent.

Hyperventilation exercise Trousseau's and Chvostek's signs, though negative at the start, became positive within 40 seconds. At four minutes, numbness of the

mouth and fingers with coolness of the knees occurred, at six minutes, stiffness of the mouth and adduction of the right thumb, at eight minutes, typical carpopedal spasm. Four minutes after inhalations of a mixture of O_2 (95 per cent) and CO_2 (5 per cent) were started, the patient returned to a normal state.

Psychiatric consultation revealed that the patient had considered herself an invalid after a doctor had told her that "she was not one of the 90 per cent who would get well."

Progress After the demonstration, the patient became convinced that the convulsions were due to her method of breathing. She was placed on a diet and given medication to increase calcium intake and to decrease the pH of the blood. Up to the present, four months after discharge, she has had no recurrence of attacks.

Case 2 A. H., female, aged 58, widow (Case 2, Chart 1)

Chief complaint Spasms of the hands and feet, duration one year

Present illness The patient first noticed symptoms while riding in an open car. She first felt irritated, then weak, then experienced numbness of her hands and later stiffness of the hands and feet. One year following her husband's death she collapsed in a theater. She had another seizure typical of tetany when she witnessed an automobile accident.

Past history Non-contributory except for information included under "Marital history."

Marital history The patient had been married at the age of 24, she had one son. As a family, they were affectionate. She and her husband were always told that they appeared very young, and she dressed accordingly. When her husband died, she realized that she was not young, and she felt, because her son was to be married, that she had little to live for.

Physical examination Findings were within normal limits. The overuse of cosmetics was obvious. Neurological examination showed hyperactive reflexes.

Laboratory tests Results were well within physiological limits. For report of blood-chemistry see chart 1.

Hyperventilation exercise At 16 minutes, band-like headache, at 18 minutes, patient felt weak, at 21 minutes, she had numbness of both hands, at 22 minutes, paresthesias were noticed, at 23 minutes, carpopedal spasm of both hands occurred. Chvostek's sign although negative before, became positive 3° bilaterally, the reflexes were markedly increased.

Course Within one month after entry, her depression regarding the death of her husband and fear for the future had disappeared. Two attacks started, but she was able to prevent spasms by holding her breath and "counting to ten." Within two months self-control had been completely regained.

Case 3 M. R., female, aged 21, single

Chief complaint Convulsive seizures, duration six weeks

Present illness The patient had periods of fatigability followed by irritability and then flushing of the face, chest and arms, terminating in headache. Seven weeks prior to entry she noticed that she had swollen eyelids and a distended abdomen. She sought medical advice and a vaginal examination was made in the course of the investigation, abdominal cramps followed this. She then noticed that her jaws became stiff, and that her hands and arms ached. The next day her hands and feet became stiff, and every day after that she had four or five such attacks, which were carpopedal spasms. Systems The patient had had insomnia, distention of the stomach, and nocturia once or twice nightly.

Physical examination Findings were normal, including neurological examination, save for slightly dilated pupils and hyperactive reflexes.

Laboratory tests and roentgen-ray examination Urine, blood and spinal fluid were normal Wassermann and Kolmer reactions were negative Encephalogram showed no abnormality Glucose tolerance test was within limits of normal Gastric analysis showed the following figures for free acid Fasting 90°, 1st specimen, 0°, 2nd, 20°, 3rd, 40°

Hyperventilation exercise reproduced her symptoms, and these were relieved by inhalations of CO₂

Follow-up report The patient returned after six weeks, at this time feeling well She was examined by an obstetrician who made a diagnosis of pregnancy, whereupon she had another attack of tetany from which she recovered When last seen she had been well for three months on an acid-ash diet and ammonium chloride

Comment This patient's condition was a rather typical example of hyperventilation tetany without other symptoms Her neurosis was initiated by the collapse of a romance because it conflicted with her almost mid-Victorian ideals of conduct The original cause has not been removed, but she is symptom-free because she knows how her symptoms are produced and can prevent them

Case 4 C C, female, aged 42, single (Case 3, Chart 1)

Chief complaint Muscular cramps of the hands and feet

Present illness The patient had a feeling of air-hunger accompanied by dyspnea, numbness of the hands and feet, and then spasms of the hands and feet similar to carpopedal spasms

Physical examination Findings were normal throughout, including activity of reflexes

Hyperventilation exercise reproduced her attacks, which were controlled by inhalations of carbon dioxide Ammonium chloride was of little value, the best results were obtained by conscious control of respiratory frequency

Remarks This case is introduced to show that some patients respond to one type of therapy when the usual methods fail This woman's neurosis was controlled without the aid of measures usually classified as psychotherapeutic

Case 5 N A, female, aged 17, single

Chief complaint Generalized eczema, malnutrition, and spasms of the hands and feet

Past history This girl had a definite family history of allergy, and over a period of years she had been suffering from intermittent attacks of an allergic dermatitis which had responded indifferently to local treatment She was subject to attacks of general malaise, cough, dyspnea, and pain in the chest accompanied by a sensation of air-hunger She hyperventilated and developed carpopedal spasms with paresthesias of the hands and feet

Physical examination Poorly developed and poorly nourished girl with crusted lesions over the neck and face Her condition was normal otherwise save for hyperactive reflexes

Laboratory tests The urine was acid The blood was normal Serum calcium 107 mg per cent Blood iodine No 60 (normal No 110) Basal metabolic rate 6 per cent minus She was found to be somewhat sensitive to cereals and to carrots

Hyperventilation exercise Tetany could be produced volitionally and controlled by holding her breath The patient was able to control, also, all other spasms by this method

Comment This patient is presented to illustrate two types of response of the autonomic nervous system the allergic manifestation, which is said to be of the parasympatheticotonic group, and the tetany, which is thought to be a sympathetico-tonic response Her neurosis was thought to be due to restrictions of her social life

because of her long standing skin disease The cause of the neurosis was not removed completely, but abatement of the skin lesions through treatment helped considerably

GROUP II

Evidence of Generalized Muscular Irritability without Actual Tetany

Case 6 B K, female, aged 40, married

Chief complaint Headache over the right orbit

Present illness At times this headache was likewise felt over the entire right side of the head She had nervousness and irritability which were made worse by the taking of citrate of magnesia for chronic constipation These symptoms were aggravated by visits to her mother-in-law

Physical examination Negative throughout save for hyperactive reflexes and 1° Chvostek's sign

Laboratory tests The urine was alkaline The blood was normal Gastric analysis showed absence of free acid in the fasting specimen and following an alcohol test-meal, and 46° after administration of histamine The basal metabolic rate was 15.4 per cent minus

Progress The patient's symptoms were controlled by medical therapy but at no time were there more alarming symptoms than those mentioned in the "present illness" It was felt that if medical therapy had not been instituted she would have progressed to a convulsive state

Case 7 L S, female, aged 53, married

Chief complaint Nervousness and irritability for seven years

Present illness After menopause and its symptoms had disappeared, this woman had a severe injury to her hand which occurred on the day of her mother's funeral Since that time she had suffered a feeling of impotence and weakness, with trembling and profuse sweating

Physical examination Restless patient, with hyperactive reflexes Blood pressure 176 systolic and 110 diastolic Normal intercourse had been impossible because of sclerosed hymen

Laboratory tests Urine and blood were normal Gastric analyses showed free acid to be absent after administration of alcohol and histamine

Hyperventilation exercise caused merely irritability and trembling, there were no symptoms of spasm

Progress This woman improved following the use of dilute hydrochloric acid with her meals, and sodium acid phosphate 0.3 gm, three times daily

GROUP III

Severe Convulsive State Simulating Grand Mal

Case 8 H B, male, aged 27, married (Case 11, Chart 1)

Chief complaint Convulsions during past eight years

Present illness While painting his car, the patient fell unconscious and remained so for nearly 45 minutes On recovery he felt weak and stiff There is no history of incontinence of urine or stool The patient had had no injuries During any excitement or following any argument, these attacks recurred As described by his wife, during attacks the patient became pale and fell to the ground with generalized tonic and clonic convulsions These episodes had no apparent resemblance to carpopedal spasm The patient had similar attacks at night In recent years he has injured his mouth in these spasms

Past history The patient was a coffin-maker He had been married for the second time, his wife was frigid

Physical examination Thin, asthenic male who appeared to be younger than stated age. The findings were normal save for Chvostek's sign of 1° on the right and 2° on the left.

Hyperventilation exercise At 5 minutes, numbness of hands and feet, at 9 minutes, adduction of the right thumb, at 11 minutes, carpopedal spasm, at 13 minutes, generalized tonic and clonic convulsions with spasm of the masseter muscles. There was no incontinence.

Laboratory tests Negative throughout save as shown in chart 1.

Progress The convulsions were not controlled until he was placed on an acid-ash regime, with calcium and parathormone. It was noted on his return visits that the time-interval between attacks became greater and the degree of response to the hyperventilation was much less.

Case 9 M L, female, aged 29, married

Chief complaint Convulsions, duration 9 months

Present illness Generalized muscular irritability preceded the onset of tonic spasm with opisthotonus. There followed clenching of the fists with kicking of the feet. Next, precordial pain occurred, with radiation down the right arm. The patient never injured herself, and had no incontinence. The seizures occurred every 4 to 6 weeks, and usually followed altercations with the family.

Physical examination Reflexes hyperactive, otherwise negative.

Laboratory tests Examinations of urine, blood, stool, and spinal fluid, and gastric analysis were negative. Basal metabolic rate 67 per cent minus. Roentgen-ray examination showed no evidence of an intracranial lesion.

Hyperventilation exercise produced trembling, dizziness and a feeling of faintness, and reproduced the tonic state described above which was not a form of tetany. Her husband said that this response was the same as that which occurred in her attacks. Before hyperventilation, examination of urine by Folin titration method showed 150° (c c 0.1 normal NaOH), and after hyperventilation, 36°, which indicates a definite shift to the alkaline side.

Comment This patient, although in a general convulsive state, has a history which suggests hysteria. She improved after developing self-control of this mechanism, and has had many less seizures.

GROUP IV

Localized Spasms of Muscles, with Symptoms Simulating Those of Cardiovascular Disease

Case 10 F S, female, aged 27, married (Case 10, Chart 1)

Chief complaint Precordial pain for 1½ years

Present illness This patient suffered weakness, easy fatigability and twitching of the muscles of the body for a short time prior to the onset of the chief complaint. She then noticed severe pain over the precordium, which radiated down the left arm. There was no dyspnea until later, but she had nausea and eructation. Just before entry a right occipital headache developed with some photophobia.

Physical examination Thin, nervous woman who cried easily. She appeared to be of the stated age. Her heart was not enlarged, sinus arrhythmia was present, there were no murmurs. Blood pressure systolic 110, diastolic 80. Reflexes were hyperactive. Chvostek's sign was 1° on both sides.

Laboratory tests Blood and urine were normal. Tuberculin test was negative. Phenolsulphonephthalein test total 60 per cent. Mosenthal test showed no fixation and good concentration. Electrocardiogram showed evidence of sinus arrhythmia and T-waves diphasic in Leads I and II, inverted in Lead III.

Hyperventilation test At three minutes, tachycardia, at eight minutes, hysterical crying, at eleven minutes, stiff lips and numbness of hands, at 15 minutes, adduction of the left thumb, at 17 minutes, carpopedal spasm, and pain recurring over the heart. See chart 1 for reports of blood and urine chemistry

Comment This patient's neurosis was based on fear. Her brother-in-law had killed his wife and his wife's family. The patient feared that her husband would do the same. The combination of psychic purgation and the use of ammonium chloride were sufficient to control symptoms of the complaint for three months

Case 11 J. A., female, aged 32, married (Case 4, Chart 1)

Chief complaint Precordial pain for two years

Present illness The patient had onset of acute pain over the precordium, felt particularly on effort. There was radiation of the pain to the left scapula. Attacks of diarrhea followed these bouts of pain, which occurred also when the patient was present at public gatherings and after she drank alcoholic beverages. Before entry she noticed stiffness of the hands and feet without actual spasms of the muscles.

Physical examination Negative throughout except for the hyperactive reflexes and a positive Chvostek's sign bilaterally.

Laboratory tests See chart 1 for all positive findings. Stools were negative for organisms and parasites which cause diarrhea.

Hyperventilation exercise At the end of 21 minutes there was a reproduction of the symptoms of pain in the region of the scapula and precordium, also of the numbness and stiffness of which she had complained. The Chvostek's sign was 3° bilaterally.

Comment This patient's neurosis was founded in dislike of her father-in-law. She was led to understand the source of her symptoms, and to be able to control them through regulation of her respiratory rate. She was placed on the acid-ash regime. Her symptoms disappeared and did not recur. The cause of this patient's neurosis could not be removed.

Case 12 D. G., female, aged 35, married (Case 13, Chart 1)

Chief complaint Rapid heart rate and precordial pain

Present illness This patient noticed that after emotional upsets and altercations, she was unable to inspire enough air for her need. Later she had onset of severe and persistent tachycardia without palpitation. A distressing tension was felt about her heart without actual pain.

Physical examination Reflexes were hyperactive, Chvostek's and Trousseau's signs were negative.

Laboratory tests For the positive findings, see chart 1.

Hyperventilation exercise At three minutes, dryness of the mouth, at five minutes, stiffness of the hands and feet, at 10 minutes, diaphragmatic constriction with momentary pain under the left breast simulating the chief complaint. Hoffmann's, Chvostek's and Trousseau's signs remained negative.

Comment As the cause of this patient's neurosis was never discovered, it is doubtful that permanent cure was effected. However, at her last visit, she had been symptom free for one month.

Case 13 M. M., female, aged 36, divorced (Case 15, Chart 1)

Chief complaint Palpitation and precordial pain, duration one year

Present illness Following the nursing of her mother through a fatal attack of angina pectoris, this woman had insomnia for three weeks and lost 16 lbs. in weight. She suffered an attack of palpitation which was mitigated by quimidine. She developed pain over the precordium pressure-like in character, which radiated to her left elbow.

Physical examination The patient had the physical signs of rheumatic heart disease with mitral stenosis and insufficiency

Laboratory tests Results are recorded in chart 1 Electrocardiogram showed evidence of delayed A-V conduction, slurred Q-R-S complexes and upright T-wave in Lead IV

Hyperventilation exercise produced rapid heart-rate in addition to the symptoms of the chief complaint

Comment This case shows that a neurosis may overlie organic disease, making it difficult to evaluate the symptoms of the organic lesion However, the patient clinically did not have the type of heart lesion that would be expected to give rise to the symptoms of which she complained In such instances the patient, even though symptom-free, should be kept under observation in order to follow the progress of the organic disease

Case 14 M M, female, aged 23, married (Case 16, Chart 1)

Chief complaint Rapid pulse and pain over heart

Present illness Following the death of her father, this woman became irritable, but it was not until after the birth of her child that she noticed rapid heart rate and pain over her heart experienced on effort She had dyspnea on exertion The pain did not radiate to her arms or neck She did not have the symptoms of irritability that had bothered her at first

Physical examination Negative save that the patient was very nervous and was observed to sigh frequently during the course of the examination

Laboratory tests See chart 1 for changes after hyperventilation Free acid was low in the gastric content (between 4° and 8° even after injection of histamine)

Progress The patient's recovery was more protracted than that of most patients, administration three times a day of 8 gm of ammonium chloride after meals and hydrochloric acid 1 cc with each meal were required After two months on this regime she had no tachycardia and only occasional episodes of hyperventilation

Case 15 T W, female, aged 35, widowed

Chief complaint Palpitation

Present illness Following the injection of novocaine for some dental work the patient had a hysterical attack of crying which ended in a tetanoid spasm accompanied by paresthesias Her father died from coronary occlusion, and throughout his illness the patient nursed him Shortly thereafter, she became subject to pain over the precordium which did not radiate to the arms but which was associated with the symptoms of fatigue, paresthesias and stiffness of the extremities These attacks occurred when she was emotionally distressed, particularly about finances and about her health

Physical examination The patient had a splenomegaly, the cause of which was not discovered, she had hyperactive reflexes and a 1° Chvostek's sign

Laboratory tests Essentially normal results were obtained throughout

Hyperventilation exercise produced the typical carpopedal spasm after 38 breaths were taken The symptoms of the chief complaint were reproduced These were relieved when the patient held her breath Exercise for determination of cardiac efficiency produced the same symptoms

Comment This patient is another illustration of the hyperirritable individual who assumes the symptoms of the illness of a person with whom he has had intimate contact It is felt that these symptoms are not imagined, but are really manifestations of local spasms of the intercostal muscles and possibly of the diaphragm

GROUP V

Vascular Disturbances Pseudo-Raynaud's Disease

Case 16 M T, female, aged 54, widowed

Chief complaint Numbness of the hands

Present illness This woman had had considerable difficulty with her husband and had been separated from him before he died. She suffered from irritability, faintness, easy fatigability, and paresthesias of the hands. Later she noticed that when she was excited, the fingers of both hands became blanched in corresponding areas. These changes occurred likewise on exposure to the cold. Still later she began to have a feeling of air-hunger and a choking sensation in the throat.

Past history In 1924 this patient had a sub-total thyroidectomy for Graves' disease. At that time she had positive eye-signs, an enlarged thyroid gland with a bruit, and basal metabolic rates of 59.5 and 22.9 per cent respectively on two occasions. At operation she was found to have a thyroiditis. In September 1927, her basal metabolic rate was 7.5 per cent minus.

Physical examination The patient had nothing about the hands which suggested capillary instability. Her reflexes were active.

Laboratory tests Negative save that gastric analyses showed no free acid in the fasting contents and only 8° after histamine was administered.

Hyperventilation exercise reproduced the blanching of the fingers bilaterally in corresponding positions, the areas increasing with the degree of hyperventilation. The same reaction was produced by immersing the hands in cold water.

Comment This patient apparently illustrates the spasm of vessels to a marked degree. The reaction did not cause a true tetany but only a stiffness of the hands. She was placed on NaCl, 1 gm. three times a day and HCl given by mouth, and her vascular disturbances have decreased considerably although they have not as yet entirely disappeared. We have observed several patients in the clinic who presented local blanching and cyanosis of the fingers (Raynaud's syndrome) whose local symptoms cleared promptly upon holding the breath or breathing CO₂.

GROUP VI

Disturbances Simulating Diseases of the Chest, Mainly of the Asthmatic Type

Case 17 C D, female, aged 55, married (Case 14, Chart 1)

Chief complaint This woman had a sense of choking and suffocation at the onset of her menstrual periods. No other symptoms occurred until she was 45 years of age when she suffered pain down her arm and paroxysmal dyspnea. She was observed at this time and has been examined frequently since for angina and more recently for coronary disease. No definite evidence has been found of the existence of coronary disease. These symptoms became worse when she had to care for her paralyzed husband whom she did not love and who was 20 years older than herself. She suffered extreme weakness and easy fatigability and had a sensation of clutching compression of the throat which would cause her to gasp for air. She had pain down the left arm during severe seizures.

Physical examination showed hyperactive reflexes. The cardiac findings were within normal limits.

Laboratory tests See chart 1 for reports of chemical tests on the urine and blood. Basal metabolic rate 32.6 per cent minus. Electrocardiogram showed left axis deviation and flat T-waves.

Hyperventilation exercise At 60 seconds there was fixation of the diaphragm, at 80 seconds, cyanosis of the nose and fingers, at 90 seconds, marked spasm of the bronchial and tracheal muscles, with a generalized convulsive spasm of the bronchial

and tracheal muscles, with a generalized convulsive seizure in an effort to regain breath. During the process she developed a 2° Chvostek's sign. Trousseau's sign remained negative.

Comment As well as being an excellent example of simulated asthma, this patient was remarkable because of the exact regularity of the cycle of her reactions. One could predict within the second what type of response would occur. She recovered rapidly following inhalations of CO₂, and has remained without major symptoms on an acid-ash regime.

Case 18 M H, female, aged 45, separated

Present illness The patient had symptoms of fatigue and weakness, paresthesias, and stiffness of the hands and feet. She came to the Clinic with the complaint of a sensation of constriction in the neck, and a lump was noticed there. She was thought to have thyrotoxicosis. Constriction of her throat caused considerable dyspnea and attacks similar to those of asthma.

Physical examination A small nodule was found at the left lower pole of the thyroid. There were no signs of toxicity, however.

Laboratory tests Urine and blood were normal. Basal metabolic rate 64 per cent minus. Gastric analysis 17° free acid in the fasting specimen, with normal response to instillation of alcohol.

Hyperventilation exercise produced paresthesias of the hands, increase of reflexes and a sensation of constriction of the throat.

Progress No observations were recorded as to the results of therapy. This patient was less troubled by her symptoms than was the patient described above (Case 17).

Case 19 J B, male, aged 46, married

Chief complaint Dyspnea

Present illness This man had epigastric pain simulating that of ulcer of the duodenum, and he had been treated with alkalis for years. He became a morphine addict, and he contracted syphilis. Because of fear of his disease he became irritable and had dyspnea on exertion. Later he began to have a tense feeling in his throat. He had constipation because of his morphine addiction.

Physical examination Findings were normal in every respect.

Laboratory tests Urine was alkaline. Blood was normal. Spinal fluid examination was negative. Roentgen-ray examination. Gastrointestinal series was negative. Gastric analysis. Normal amount of acid.

Ventilation was observed and the symptoms were seen to increase in the process. A formal experiment was not performed.

Progress Response to treatment was not rapid here because of the morphinism. Some improvement was noted after reassurance was given, as well as after the use of the acid-ash regime.

GROUP VII

Simulation of Thyrotoxicosis

Case 20 L J, male, aged 25, single

Chief complaint Numbness of the hands

Present illness For two years the patient had experienced nervousness, tachycardia and palpitation. He was easily fatigued. His basal metabolic rate was 14 per cent plus, and a subtotal thyroidectomy was performed. Following this operation, symptoms of tachycardia and palpitation decreased but the paresthesias of the hands persisted.

Physical examination Asthenic male with hyperactive reflexes

Laboratory tests Blood and urine were normal Gastric analysis showed an absence of free acid even after injection of histamine Basal metabolic rate, 34 per cent minus

Hyperventilation exercise reproduced the symptoms of the hyperthyroidism and the paresthesias of the hands

Progress The patient was placed on a high salt intake and improved slightly He was then given HCl by mouth

Comment This man and others of this group are examples of a type of patient appearing in the thyroid clinic who is not thyrotoxic but who has a neurosis giving similar symptoms

Case 21 M M, female, aged 37, married

Chief complaint Nervousness following an operation

Present illness The patient had been nervous for the past five years She had tremor, intolerance to heat, increased appetite, and a loss of 10 lbs in weight She noticed a sudden enlargement of the left side of her neck, and visited a doctor At this time she had dyspnea on exertion and nocturia On examination the left lobe of the thyroid was found to be enlarged The basal metabolic rate was 44 per cent plus An adenoma of the thyroid with hemorrhage was diagnosed, and was found when thyroidectomy was performed Six months later the patient returned to the clinic Save for the absence of the swelling, she had at this time the same symptoms that she had had at previous entry

Physical examination was negative

Laboratory tests Gastric analysis showed absence of free acid, but a normal response to alcohol test-meal

Hyperventilation exercise reproduced all of her symptoms

Progress This patient improved greatly following the use of ammonium chloride and the institution of an acid-ash diet Her symptoms are now controlled The neurosis was not cured because it was caused by the marital status which has remained unchanged

Case 22 L F, female, aged 25, married

Chief complaint Nervousness and fullness in the neck

Present illness For six years this woman had noticed increasing irritability There were tremor and nervousness, palpitation, tachycardia and intolerance to heat On several occasions she had hysterical upsets

Physical examination showed an adenoma of the thyroid The basal metabolic rate was 18.6 per cent plus Radiation with roentgen-ray was begun, and two months later the basal metabolic rate was 8.5 per cent minus After four years she returned with the same symptoms It was learned that, while she was living at her uncle's home, she had a clandestine romance with him which she was unwilling to stop, and which was in constant danger of exposure

Laboratory findings were within normal limits

Hyperventilation exercise reproduced all of the symptoms of the present illness

Progress At the present time she has shown improvement under medical therapy Psychotherapy is being directed toward helping her to establish some sort of decision as to her relationships in the future This patient was not operated on, as were the former patients, but it is believed that her adenoma is not toxic

Case 23 E H, female, aged 29, married

Chief complaint Nervousness for four years

Present illness Four years ago the patient began to notice a feeling of weakness

and increasing nervousness. She had loss of emotional control. During the next year an enlargement appeared in her neck and she noticed that her heart rate was rapid and that she had increased perspiration. Treatment with Lugol's solution caused improvement. One year before entry she returned to the clinic with palpitation and dizziness. She had lost four lbs. She had dyspnea and a sense of tension in the chest on inspiration.

Physical examination There was slight enlargement of the right lobe of the thyroid. She seemed to be more nervous than the signs of thyrotoxicosis would warrant.

Laboratory findings were entirely normal.

Hyperventilation exercise reproduced the symptoms of palpitation and dizziness and the sensation of constriction in the chest.

Comment The results of treatment cannot well be evaluated here because of an involved social history which has not been completely obtained. The exercise aided in establishing a contact with the patient which has been very helpful in psychotherapy.

GROUP VIII

Gastrointestinal Disturbances

Case 24 F H, male, aged 35, single (Case 12, Chart 1)

Chief complaint Epigastric pain

Present illness This man suffered severe weakness and nervousness and muscular twitchings. He developed midepigastric pain followed by gas pains, at first occurring after meals and later having no relation at all to meals.

Physical examination Hyperactive reflexes and 1° Chvostek's sign were found.

Laboratory tests See chart 1 for urine and blood findings.

Hyperventilation exercise produced the muscular twitchings in six minutes and generalized muscular contractions in nine minutes.

Progress This man's symptoms were relieved by the acid-ash regime which of course is directly opposed to the usual method of treating peptic ulcer.

Case 25 W R, male, aged 27, single (Case 17, Chart 1)

Chief complaint Epigastric pain relieved by food

Present illness The patient's pain occurred in the epigastrium before meals and was relieved by food and soda. The pain radiated to the back under the left scapula. There was no nausea and no vomiting or melena. This man also suffered a sense of suffocation and tightening of the facial muscles when he talked or laughed too much.

Physical examination Perspiring, nervous and asthenic male appearing to be of the stated age. Reflexes hyperactive and equal.

Laboratory tests All findings were normal save that the gastric analysis showed no free acid and only 22° after injection of histamine. Gall-bladder visualization was negative. See chart 1 for reports of the blood and urine chemistry.

Hyperventilation exercise reproduced the epigastric pain and produced carpopedal spasm. Chvostek's sign 2° was observed bilaterally.

Comment This patient had obvious signs of tetany but associated with it were the symptoms of the complaint. He had suffered from atrophic arthritis and it was felt that his discouragement over the progress of this disease was the basis of his neurosis.

Case 26 R S, female, aged 45, married

Chief complaint Eructations of gas from the stomach

Present illness Since the age of 18 the patient has had gas pains for which she had taken soda and at intervals she has had periods of dizziness. Ten years before

entry, following an operation for tonsillectomy she had a recurrence of the spells of dizziness. For two years she is said to have had tarry stools following these attacks.

Physical examination Entirely negative

Laboratory tests Urine, blood and stool were normal. Gastric analysis. No free acid after instillation of alcohol, but 62° after injection of histamine. Roentgen-ray examination. Gastrointestinal series and barium enema were negative.

Hyperventilation exercise produced diaphragmatic spasm, belching and hiccoughing. This patient demonstrated fixation of the diaphragm more typically than most patients, and she had symptoms of her chief complaint at the same time.

Case 27 R S, male, aged 40, married

Chief complaint Tenderness in the epigastrium

Present illness The patient had epigastric pain first 10 years before entry, and his attending physician diagnosed peptic ulcer. The Sippy diet relieved his symptoms. Three months prior to observation he had recurrence of symptoms, and at this time a gastrointestinal series gave findings interpreted as duodenitis without gastric retention. He remained on the Sippy regime for three months and then began to have cramps in his legs, tightening of the muscles of his face and paresthesias of his hands. These symptoms happened under emotional strain.

Physical examination Thin, asthenic male who appeared to be of the stated age. Hyperactive reflexes and 1° Chvostek's sign were found.

Hyperventilation exercise reproduced the symptoms of tetany. The patient was placed on ammonium chloride 0.6 gm three times daily. He recovered from these symptoms, but in three months' time the symptoms of ulcer appeared. A neutral powder was then used so that the acid-base balance could be more finely adjusted.

Comment It was felt that this man was on the verge of alkalosis tetany and in excitement mild over-ventilation caused the tetany to occur.

Case 28 J C, female, aged 34, married (Case 1, Chart 1)

Chief complaint Irritational distress in the epigastrium, duration 1½ years

Present illness This patient, a teacher, always had symptoms following the close of the school term. At these times she had epigastric distress, easy fatigability, headache, and paresthesias of the hands.

Physical examination Negative except for hyperactive reflexes and Chvostek's sign 1° bilaterally.

Laboratory tests The urine was alkaline, the blood was normal. See chart 1 for report of urine and blood chemistry.

Hyperventilation exercise produced headache, trembling of the arms and clonus, within nine minutes.

Progress This patient improved markedly after acid therapy was instituted. Her neurosis was initiated by a marital problem which was later solved to some extent by her loss of symptoms and by an explanation of the problem.

Case 29 T P, female, aged 31, married

Chief complaint Eructations of gas from stomach, and mucous colitis

Present illness For four years this woman had had increasing nervousness and irritability, and then she had midepigastria distress with eructation and nausea. Colitis with diarrhea developed and she expelled quantities of mucus.

Physical examination A thin, poorly nourished, asthenic woman who talked so fast and inspired so rapidly that during the taking of her history she produced the symptoms of her complaint.

Laboratory tests Normal findings for urine and blood. Gastric analysis. Absence of free acid in the fasting specimen and 32° after injection of histamine. Be-

fore hyperventilation, the urine tests by the Folin titration method showed 960°, and after hyperventilation 36°, which is evidence of a complete shift to "actual alkalosis"

Progress This patient responded well to therapy directed toward production of mild acidosis. Her neurosis was based on the fear of losing her husband because of her chronic illness. This neurosis decreased with her improvement.

GROUP IX

Simulation of Diseases of the Special Senses

(Pseudo-Memere's Syndrome)

Case 30 T M, male, aged 26, single (Case 9, Chart 1)

Chief complaint Vertigo

Present illness This man had a sudden onset of dizziness and tinnitus with apparent loss of hearing in one ear, sometimes noticed on the left side, sometimes on the right. He noticed, also, a numbness of the hands with rigidity of the muscles.

Physical examination The patient was of the pyknic type. At first the findings were normal save for hemorrhoids which were removed under general anesthesia. On return from surgery, he was in severe tetany with marked nystagmus, and while he was being revived by inhalations of CO₂ and injections of calcium chloride he again complained of tinnitus and deafness.

Laboratory tests See chart 1 for findings.

Hyperventilation exercise reproduced in 12 minutes the symptoms mentioned above.

Progress This man was placed on ammonium chloride, 0.6 gm three times daily. When he was seen three months later, it was noticed that the exercise produced the symptoms after a longer interval from initiation of the breathing, and that the symptoms were not so profound. Later, after this man was married, his symptoms did not recur even when he was allowed a normal diet and when medication was withdrawn. Since this man was not the asthenic type, the true nature of his disturbance was not suspected until the symptoms occurred following the anesthesia. Other examples of this type of functional disturbance have been observed, and those patients have responded to the same measures.

GROUP X

Organic Disease (Coronary Occlusion) Producing Hyperventilation Tetany as a Symptom

Case 31 M McM, female, aged 50, married

Chief complaint Spasms of the hands with hyperpnea

Present illness Patient had increasing fatigability and numbness of one hand and arm. Later, she had pain across the precordium. She had no dyspnea, orthopnea, palpitation or tachycardia. She began to have abdominal distention but did not have nausea or vomiting.

Physical examination Heart was not enlarged to percussion. Sounds were very faint, they were regular and no murmurs were heard. Lungs were clear. Liver and spleen were not palpable. There was no edema.

Laboratory tests Urine and blood were normal. The electrocardiogram showed left ventricular preponderance, diphasic T₁, slurred QRS, notched R_s, diphasic T₂, positive S-T₁, negative S-T₂.

Course The day of entry she had an attack of distention, became slightly cyanotic, and had a definite carpopedal spasm. There was neither pain nor dyspnea. She was held to hold her breath, and without any medication the attack wore off quickly. The next morning she had another attack in which she died.

Comment We mention this patient as an interesting example of the superposition of this syndrome on the symptoms of serious organic disease. This case in itself is a warning of the constant danger of classing too many patients as neurotic, and of the need for thorough physical proof to rule out organic illness before it is concluded that the patient's condition is merely a neurosis.

GROUP XI

Suspected Neuroses Which Were Not Proved by Hyperventilation Experiment

Case 32 L P, female, aged 45, married (Case 5, Chart 1)

Chief complaint Pain over precordium

Present illness This patient had attacks of weakness and dizziness which occurred at increasingly frequent intervals up to the time of entry into the hospital. Several months before, she had become conscious of pain over the precordium which did not radiate to the arms but which was associated with dyspnea and palpitation.

Physical examination Sinus tachycardia was present. There was no evidence of myocardial damage.

Laboratory tests Normal findings for urine and blood. Electrocardiogram, and roentgen-ray film of the chest for determination of the size of the heart, were negative. See chart 1 for reports of laboratory work after hyperventilation.

Hyperventilation exercise failed to induce the symptoms of the complaint, nor were symptoms of tetany produced. The CO combining power was about the same as that found in other instances. She was placed on an acid-ash regime and improved as well as had other patients. It is probable that she was not exercised long enough to produce the desired results. Her neurosis was based on economic problems which were not solved.

Case 33 A A, female, aged 43, single (Case 7, Chart 1)

Chief complaint Precordial pain

Present illness Following the loss of her family, this woman had nervous irritability. Later she had pain in the left side of the chest, not radiating and not associated with dyspnea.

Physical examination Negative

Laboratory tests, including electrocardiogram, roentgen-ray studies of the chest and spine. No abnormal findings.

Case 34 R McA, female, aged 40, single (Case 8, Chart 1)

Chief complaint Hoarseness, duration 6 weeks

Present illness For 7½ years this woman had had pain in the tips of the fingers with skin lesions of a desquamating erythematous nature. She had also had numbness and stiffness of the fingers. She had had attacks of nausea and vomiting.

Physical examination Skin lesions were present which are described above. Reflexes were hyperactive.

Laboratory tests Urine and blood were normal. Electrocardiogram showed evidence of myocardial damage. Sedimentation rate 35 minutes. No evidence of arterial disease was obtained by surface temperature readings before and after administration of spinal anesthesia. Response to alcohol meal was normal.

Hyperventilation exercise did not produce the desired results because of poor cooperation on the part of the patient on the several occasions when it was tried. It will be noticed that the CO₂ combining power increased, and this may be evidence that the patient became less sensitive to nervous stimulation.

Case 35 C M, female, aged 51, widowed

Chief complaint Dyspnea, duration five years

Present illness Following the onset of irritability, this patient had dyspnea, and then precordial pain which was non-radiating in character

Physical examination Slight peripheral arteriosclerosis was present The heart was not enlarged, a soft systolic murmur was heard at the apex

Laboratory tests Gastric analysis No free hydrochloric acid even after injection of histamine Electrocardiogram showed no evidence of cardiac damage Roentgen-rays of the chest and gall-bladder were negative

Hyperventilation exercise was not successful in producing the symptoms, chiefly because of inability to gain proper cooperation from the patient She signed her release from the hospital before further studies could be made

Comment The patients of this group are presented to illustrate that the hyperventilation exercise, to be successful, must be performed when the patient is completely at ease and understands that cooperation is essential for the success of the experiment It is possible that there are patients who will not react to the experiment even though they do cooperate These may have other mechanisms which produce their neuroses or they may have organic disease, the symptoms of which are not affected by the irritating action of the hyperventilation exercise

In table 1 are compiled the results of chemical studies on the urine and blood made before and after the exercise of hyperventilation

It is to be noted that in only 10 of the 14 patients listed is the carbon dioxide combining-power shown to be reduced, as described by McCance and others^{2, 8, 11, 18} In all save two, the chlorides are increased¹³ The total calcium is normal, but in some instances the diffusible fraction is at the lower limits of normal It may be that for these individuals, the diffusible calcium is actually below their normal threshold Blood-sugar and serum-proteins are normal, but near the lower limits Magnesium studies show normal determinations for most of the patients In those in which the serum magnesium is low, the magnesium content of red blood cells offsets the effect of the loss of serum magnesium as a cause of tetany¹⁴ The most clearly demonstrable shift of pH is seen in the studies of the urine, in which the colorimetric readings show an increase of from 2 to 3 units Likewise the drop in the ammonia per cubic centimeter is nearly 50 per cent Acetone was found in only one of the specimens taken It is felt that these results show a definite tendency towards alkalosis, and that the amount is that stated by Collip² to result in tetany Because of the expense entailed in the complete analysis as given above, it was thought advisable to use a test which would demonstrate this change most simply and graphically The Folin¹⁵ pH titration method for urine may be used with good results This procedure may be accomplished with the aid of the apparatus used in titrating gastric contents With the addition of 15 to 20 gm of potassium oxalate to 25 cc of urine, the titration is made with 0.1N sodium hydroxide, using phenolphthalein as indicator The specimens taken before and after the hyperventilation experiment are so tested, and are arbitrarily considered as being part of a normal output of 1,500 cc This step is made to take advantage of the normal figures as described by Folin, which

TABLE I
Table of Laboratory Work on Patients with Hyperventilation Syndrome

Number	Patient	Social	Sex	Age	Neurosis	Symptoms	B M R	CO ₂ before HV (vol %)	CO ₂ after HV (vol %)	Chlorides before HV (mg %)	Chlorides after HV (mg %)	Calcium (total)	Calcium (diff)	Serum protein (total)	Serum albumin	Serum globulin	Blood sugar	Serum magnesium	RBC magnesium	Hematocrit	Urine pH before HV	Urine pH after HV	Urine ammonium total before HV	Urine ammonium total after HV	Urine ammonium per c c before HV	Urine ammonium per c c after HV	Urine acetone before HV	Urine acetone after HV	
1	J C	M	F	34	Inheritance ? incapability	Weakness, dizziness, dyspnea, trembling	13 2 —	53 9	44 5	—	—	10 60	5 20	8 25	3 2	5 01	88	—	—	—	—	—	—	—	—	—	—	—	
2	A H	W	F	58	Fear of advancing age, death of husband	Same as (1), tetany	—	48 5	42 0	—	—	10 50	—	—	—	—	—	2 2	—	—	—	—	—	—	—	—	—	—	
3	C C	S	F	42		Same as (1), tetany	5 0 —	54 5	44 4	617	623	11 02	10 90	6 40	4 58	2 18	99	2 35	—	—	—	6 6	7 4	—	—	—	0	0	
4	J A	M	F	32		Same as (1), precordial pain	7 6 +	53 8	44 4	594	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	
5	L P	M	F	45	Financial loss, ? home broken up	Same as (1), precordial pain, palpitation, tachycardia	3 0 —	48 5	44 7	605	594	10 12	9 92	—	—	—	99	2 5	5 2	42 8	—	—	—	—	—	—	—	—	
6	D E	M	F	24	Divorce husband, indulgent mother	Same as (1), tetany, laryngeal spasm	—	—	—	—	—	8 67	4 62	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	
7	A A	S	F	43	Lack of family protection, not married	Pain in left precordium	—	57 8	52 1	596	612	11 12	5 5	—	—	—	—	2 2	6 85	43 5	—	—	—	—	—	—	—	—	
8	R M A	S	F	10		Same as (1), tetany, dermatitis fingers toes	—	38 8	42 7	622	602	9 96	5 28	—	—	—	86	2 7	8 0	30 2	—	—	—	—	—	—	—	—	
9	T M	M	M	26	Poor finance, fear of marriage	Same as (1), nausea, tinnitus, vertigo	20 7 —	52 2	56 9	599	562	10 35	5 00	5 70	3 82	2 05	89	1 95	7 25	42 5	—	7 2	9 1	23 0	12 2	114	0 91	0	0

TABLE 1—Continued

Number	Patient	Social	Sex	Age	Neurosis	Symptoms	B M R	CO ₂ before HV (vol %)	CO ₂ after HV (vol %)	Chlorides before HV (mg %)	Chlorides after HV (mg %)	Calcium (total)	Calcium (diff)	Serum protein (total)	Serum albumin	Serum globulin	Blood sugar	Serum magnesium	RBC magnesium	Hematocrit	Urine pH before HV	Urine pH after HV	Urine ammonium total before HV	Urine ammonium total after HV	Urine ammonium per cc before HV	Urine ammonium per cc after HV	Urine acetone before HV	Urine acetone after HV
10	F S	M	F	27	Fear of husband	Same as (1), tetany, any, precordial pain, tachycardia	37—	49.3	36.0	577	604	10.20	4.23	6.64	4.48	1.98	94	2.9	4.6	43.2	5.4	6.6	36.0	26.5	40	217	0	0
11	H B	M	M	27	Finance and mother in law	Same as (1), tetany	71—	56.9	56.2	587	581	10.94	4.90	5.56	3.76	1.87	90	22.25	25.0	714.5	5.4	7.6	75.8	32.5	41	22	0	0
12	F H	S	M	35	Finance	Epigastric pain same as (1)	13.6—	53.0	55.9	582	585	9.82	4.46	6.09	4.01	2.10	91	1.8	5.6	48.8	5.0	6.8	118.0	19.7	62	33	0	0
13	D G	M	F	35	? children	Same as (1), palpitation, tachycardia	57+	43.6	48.3	584	582	10.30	4.92	5.35	3.86	2.26	98	1.7	6.3	45.7	4.8	8.0	40.7	11.2	72	22—	0	0
14	C D	M	F	55	Incapability told she was invalid by M D	Same as (1), laryngeal con- striction (has myocardial damage)	20.0—	60.6	53.1	594	617	10.00	5.33	6.09	3.79	2.28	99	—	—	—	5.8	6.8	19.6	3.64	192	113	0	0
15	M M	D	F	36	Nursed mother through anginal attack, demise of mother just prior to onset	General malaise, palpitation, dyspnea	8.4—	58.6	38.6	—	—	10.70	—	—	—	—	—	—	—	—	—	6.2	—	—	—	—	—	—
16	M M	M	F	23	Death of father, birth of baby	Pain over precor- dium, dyspnea, tachycardia	9.8—	50.1	42.6	455	418	—	—	—	—	—	—	—	—	—	—	acid alk	—	—	—	—	—	—
17	W T R	S	M	27	Not determined	Pain in epigas- trum, dyspnea and tension of facial muscles when talking	—	48.2	40.7	584	585	—	—	—	—	—	84	—	—	—	—	5.7	7.2	—	—	—	—	—

are 200 to 500° 0.1/N sodium hydroxide for that amount Folin states that any figure under 250 is a good indication of actual alkalinity So far, this test has proved satisfactory in that it shows a definite shift to "actual alkalinity"

Some explanation should be made for the almost insignificant changes in the figures which represent the shift in acid-base balance In subsequent publications, Dr Mayo H Soley of our clinic and Dr N W Shock of the Department of Biochemistry are to report the results of biochemical studies on similar patients, made in an attempt to gain more accurate data upon the rapidly changing shifts in the acid-base equilibrium and the gaseous exchanges through the lungs They have found that the shift in pH of the blood is greater than has been indicated in the past, and that the reaction is a rapid one They suggest that the indefinite results heretofore obtained are caused by the ungainly technic of venipuncture The general trend of their results supports the contention that there is a definite alkalosis present when hyperventilation takes place

In reviewing the histories of 50 patients, listed since 1928, in which the diagnosis of psychoneurosis with anxiety neurosis was made, figures were compiled which are shown in table 2 From the description of the

TABLE II

Since 1928, fifty patients have been admitted to the University of California Hospital whose conditions have been diagnosed as psychoneurosis with anxiety neurosis

No of patients with symptoms similar to the ones now described as associated with hyperventilation	36
No of patients without these symptoms	14
No of patients with the following symptoms	
Weakness and fatigability	18
Numbness and paresthesia	14
Palpitation and increased cardiac rate	12
Dizziness	10
Nausea and vomiting	4
Muscular contractions	
Twitching, trembling, convulsive states	14
Tetany (not on basis of hypoparathyroidism)	9
Difficulty in swallowing, talking, breathing (pharyngeal-laryngeal spasm)	8
Precordial pain (intercostal muscle and diaphragmatic spasm)	4
Dyspnea (diaphragmatic spasm)	14
Epigastric pain (diaphragmatic spasm)	2
Constipation (spastic colon)	5

The figures given above are compiled from the descriptions of the symptoms and signs that are given, and not from the results of formal experimentation

symptoms and signs alone, nearly 70 per cent of the patients classed as psychoneurotic were found to have symptoms of hyperventilation tetany, either local or general

DISCUSSION

In attempting to show the mechanism which is responsible for this sequence of events, we have constructed a diagram illustrating the physiological and biochemical changes which apparently form the background of

The chief response is through the sympathetic nervous system, the reaction of the parasympathetic system is less apparent¹⁶ Through the sympathetic system there is stimulation of the peripheral vascular bed, with spasm of the arterioles, and through impediment of the circulation a tissue anoxemia is produced which, according to Davies, Haldane and Kennaway,¹⁷ causes increased muscular irritability, and thus increases the peripheral sensations These authors have shown that this type of tetany can be relieved by oxygen inhalations Bazett and Haldane¹⁸ found that the hyperpnea due to hot baths can be relieved by a mixture containing 14.2 per cent oxygen and 8.5 per cent carbon dioxide Hill and Flack¹⁹ demonstrated that the hyperventilation of oxygen would not cause convulsions even when the alveolar carbon dioxide was reduced to 1.47 volumes per cent Certainly tissue anoxemia is an exciting factor in the production of muscular irritability, and thereby it can produce tetany

The stimulation of the members of the endocrine system is the second mechanism set in motion by the impulses coming in over the sympathetic nervous system Stimulation of the pituitary gland has, for its chief effect, the reactions which follow increase in water retention by the tissues, with subsequent storage of sodium ions and production of alkalosis and tissue hydremia The work of Furstenburg,²⁰ and, in an earlier period, of McQuarrie,²¹ is mentioned here because of the low total protein and serum albumin which was found in all but one of the patients listed This may be an indication of increase in hydremia, and if so there might be an increase in alkalosis through the presence of sodium ions

The best known effect of the sympathetic stimulation upon the endocrine system is that of the adrenals This stimulation, and the increase in the flow of adrenalin through the system, directly affects the substance of the nerves According to Bonnet, Franck and Richard,²² there is an increase in the summation of impulses, but no effect on the chronaxie of the nerve With repeated stimulation, smaller impulses cause the discharge of the cycle of symptoms grouped as the complaints of these patients Adrenalin is, of course, a cerebral cortical stimulant as well as a respiratory and cardiac accelerator by central action

The stimulation from hyperventilation is most likely central in origin Although no reports were found of studies in which adrenalin had been used, the work of Hammouda²³ throws some light on the question This investigator found that, when he used heat as a stimulus, he was unable to produce panting in dogs by its application to any of the peripheral sensory endings in the rib-cage or its viscera The only central nervous area that responded was the optic thalamus Whether adrenalin acts at this point is, at present, a matter of conjecture

A number of physiologists have studied hyperventilation in man From the work of Collip and Backus,² McCann,⁵ Grant and Goldman,³ and from the observations reported in this paper, it is felt that the mechanism centers

chiefly in the $\frac{\text{HCO}_3}{\text{NaHCO}_3}$ buffer and its variations with the exhalation of carbon dioxide from the lungs. With this change, NaHCO_3 is left in the blood stream. This base is usually eliminated through the kidney, but the process is not fast enough to prevent some of it from being deposited in the muscle. In an effort to maintain the acid-base equilibrium, there is a reduction in the formation of ammonia²⁴, hence less is excreted, as is shown in table 1. There is likewise a retention of phosphates and of chlorides^{11, 13}. In all probability there is withdrawal of chlorides from the stomach for this purpose, which would explain the absence of free hydrochloric acid in the stomachs of these patients when tested. The muscles themselves add lactic acid to the equation. In some instances, acetone has been recovered¹⁷ which is probably shielded by some of the alkali and excreted before normal oxidation can take place. Our findings are less constant in these respects than those of other authors^{2, 5, 11, 18}. All of these attempts to acidify the tissues are insufficient, and the tissue alkalosis persists with subsequent hyperirritability of the muscles which finally leads to tetany.

According to Brody,²⁵ hyperventilation will definitely increase the irritability of the cortex, possibly because of tissue alkalosis. Brody feels that there may be some other factor as well. However, hyperventilation affects the patients described above in greater degree than it ordinarily does those people who overbreathe voluntarily. It is felt that this difference is due to the synergistic effect, described by Brody, occurring when hyperventilation is instituted after previous cortical stimulation from other sources. In such a state as that of fear or of any of the emotional reactions, adrenalin is probably the cortical excitant, instead of strychnine which was used by Brody.

The stimulation of the cardiac center by adrenalin causes an increase in the rate-volume output of the heart, after preliminary slowing of the heart due to an initial rise in blood pressure. However, when hyperventilation is present the results are more complex and somewhat more variable. McDowell²⁶ found that, when carbon dioxide is washed out of the blood stream by hyperventilation, there are two effects: (1) vasodilation due to central vasomotor control stimulation, and (2) vasoconstriction due to direct action on the peripheral vascular bed. In some patients the first mechanism seems to be in control, in others the second seems to predominate, and in still others there seems to be a balance, so that a variety of changes in the blood pressure and sensations due to change in the peripheral vascular bed may be predicted because of the variety of responses in adjacent areas. The important principle to remember is that this variety of reactions has the same cause, and can be managed according to the same regimen of treatment. Roome²⁷ supports the contention made by McDowell, and states that the addition of 5 per cent carbon dioxide to the inspired air will control these changes in the

peripheral vascular bed According to McDowell, in animals this response is definitely attributable to a local chemical action and not to a nervous one, for there is no evidence of nervous stimulation such as dilation of the pupil or acceleration of the heart rate However, in human beings there is little doubt, from the emotional nature of the onset of the disturbance, that the action of adrenalin is also a factor, and that the hyperventilation is more or less involuntary—at first as a natural sequel to the emotion It is easy to see that local anoxemia may exist and be a factor in the cause of tetany No studies have been made on the content of oxygen in the capillary blood supply to these regions, so that there is no definite proof of this statement However, Striker, Goluben and Tarchanoff²⁸ have shown that alkalization of capillaries by local application will cause constriction of the vessels of the bed Severini and Krugh²⁸ stated that carbon dioxide will dilate the capillary bed In cases of spasm, the constriction remains until muscle metabolites form to reduce the pH at that point, and then the spasm relaxes

In connection with this syndrome, the presence of the symptoms of hyperthyroidism has been noted in patients seen in the authors' clinic These patients have been treated by psychotherapy, and have improved It is believed, however, that they suffer from this syndrome rather than from direct stimulation of the thyroid There is no chemical evidence of any effect on the parathyroids The stimulation of the gonads is a matter of conjecture No observations on this subject have been made, although it is evident that work should be done It is possible that in the sexual act, the orgasm is, in a sense, the result of hyperventilation tetany In the process there is increase in the respiratory rate, increase in the irritability of the muscles that control the act of erection, and finally there is tonic spasm of the muscles of the sexual organs and of the skeletal system as well How studies can be made under these conditions remains to be discovered, at any rate, the problem warrants consideration

It is suggested by the work of Pottenger¹⁶ that in addition to the suppression of free hydrochloric acid, dilation of the stomach and contraction of the sphincters would cause symptoms increasing the neurosis The same is true of the effect on the urinary bladder, gall-bladder and renal pelvis in these patients who are really suffering from a form of sympathetico-tonia There is spasm of the internal sphincter and trigone, and dilation of the bladder These symptoms, together with those resulting from direct cortical irritation, are sufficient to augment the neurosis, they cause the patient to feel ill, and thereby stimulate anxiety about his health—and the vicious cycle becomes complete Repeated cystoscopy, or other local treatment, tends to augment changes in the mucous membranes and leads to further structural change

It is well at this point to mention that another form of physiological disturbance has been observed in the psychogenic upset described above Two patients were seen who had been so stimulated that hyperhidrosis occurred

which was severe enough to cause a hypochloremia similar to that found by Piersol and Karr²⁹ in postoperative vomiting, in complications of peptic ulcer, and in hypertensive heart disease following the use of low salt diets. This portion of the subject is to be enlarged upon and reported at a later date.

The subject of seasickness, car-sickness (from riding in street cars, motor cars, and other rapidly moving conveyances), and air-sickness has attracted our attention over a period of several years. The close connection between the labyrinth, muscles of the eyes, and the gastrointestinal tract is well known. From personal observations upon many subjects in this group, it became apparent that anxiety is a significant factor in preparing the individual for the episodes which are so distressing to travellers. It is not assumed that certain subjects may not have over-sensitive labyrinths, or functional disturbances in the several structures participating in the production of these symptoms. However, the fact that most persons can become accustomed to the motions of conveyances, and the well known beneficial action of certain measures used in prevention and treatment (namely, sedatives such as bromides, antispasmodics such as atropine, peripheral dilators such as the nitrites, and inhalation of carbon dioxide) suggest that the anxiety state is more important than is generally appreciated. The termination of a bout of seasickness after several days may be promoted by the production of acidosis which compensates for the alkalosis induced by prolonged vomiting and anxiety combined.

Another problem—one which confronts those engaged in commercial conquest of the stratosphere—relates to altitude-sickness. Unless this problem is solved, the hazards of prolonged flight at altitudes above 12,000 feet will retard development. So far, attention has been centered chiefly in the reduced oxygen tension at high elevations. We proposed some time ago that a careful study be made of the concentration of carbon dioxide in the cabins of airplanes at these high altitudes. If ventilation is maintained and supplemented by oxygen and the carbon dioxide is lost, it would appear that subjects would suffer. Theoretically, if the respiratory mechanism is to function adequately, the carbon dioxide concentration should be kept at a higher level than normal. Experiments with this point in mind should be performed. The symptoms suffered by many of the subjects studied suggest a state of alkalosis.

The subject of hysteria is of historical and practical interest. It is our opinion that theoretically the episodes can in many instances be explained by the presence of the anxiety state, with extreme effects upon the psyche and periphery. The stocking-and-glove anesthesia is more likely a disturbance caused by limitation of the blood supply to the peripheral nerves, than due to central effects upon the peripheral nerves themselves. One cannot exclude blocks in the somatopsychic pathways wherein the registration of sensation from the periphery is wanting.

TREATMENT

Treatment of patients suffering from this condition should be divided into two types palliative and curative. The latter procedures consist of the use of psychotherapy by such means as psychocatharsis, reeducation, reassurance, and the substitution of a "non-fear" meaning in situations where desensitization is needed. The palliative measures or medicaments have very definite use for several reasons. Through immediate relief of symptoms, part of the cause of the neurosis is removed—namely, that portion dealing with the patient's concern regarding his health. He feels well for the first time in months, and therefore the emotional rapport with the physician is made stronger, so that the psychiatric procedures mentioned above may be performed much more easily. Also, the demonstration illustrates to the patient the mechanism of the physiological difficulties which he himself has caused, and the results are so dramatic that he is able to follow the procedure and to appreciate what the results mean to him. He is then in a position to check the physical changes at an earlier period, and to save himself from more profound disturbances.

The use of any agent that will break the course of events described in chart 1 will accomplish this purpose. The first group of measures are those which help to control the acid-base balance. These were used in the patients of our series. The inhalation of oxygen-carbon dioxide gas (70 per cent O to 30 per cent CO₂) is most effective³⁰ both in speed and adequacy. When the apparatus is not at hand, a paper sack inverted over the patient's head and sealed with adhesive tape, is successful. Some patients have responded to drinking small quantities of carbonated water or beer. Although these methods work well in convulsive attacks, it is found of advantage also to place these patients on an acid-ash diet, to reduce the fluid intake to 500 c c, and to administer ammonium chloride in dosage^{30, 31} as large as one gram, given by mouth in capsules from three to six times a day. A suitable prescription is as follows:

Ammonium chloride	30 0
Fld ext licorice	20 0
Syr yerba santa	75 0
Cinnamon water q s ad	120 0
Sig One teaspoonful 3 to 6 times per day	

Or, simply the use of the *Mistura glycerhizae co* as the vehicle is successful. Chloride ions may not be as effective as carbon dioxide for Douglas and Havard³⁰ have shown that carbon dioxide permeates the respiratory center more quickly than chloride ions.

The next two methods are projected for future work. The first of these is based on the work of Levy and Ditz³² whose studies were limited to the phenoxyethylamine and orthomethoxyethylamine compounds. They tested the action of drugs in these groups on the heart action and respiratory rate in dogs, on the intestine *in situ* of the dog, and on the isolated intestine of

the guinea pig They followed the metabolism of the glucoside in the rabbit, and the toxicity by intravenous route in the mouse Of the group of eight drugs, there is one that will prevent vasoconstriction, inhibition of intestine, and increase in the respiratory rate—and that compound is *phenoxyethanolamine 2 ethane* This preparation has to be given prior to the expected extravasation of adrenalin, and is really preventive rather than curative So far as is known, this group of drugs has not been used in the treatment of human beings Other better known drugs have been used these are ergotamine, yohambin, hydrastin and quinine Their use is preventive also

Another method is suggested by Pottenger's reports¹⁶ After proving, by the tests he has outlined, that a patient is sympathicotonic, one might endeavor to develop parasympathetic tone in opposition to the former state Pilocarpine, histamine, and acetylcholine are suggested by this author as a means of attempting to convert these people to a more median type A difficulty arises here because some people have excess in both systems, and this method would aggravate symptoms of parasympathetic tone which do not form a part of the picture described above

SUMMARY

The authors believe that there is a physiological background for the perseverance of an anxiety state as part of a psychoneurosis, that this background is produced by the constant presence of purely emotional disturbances, and that the resultant physiological state aggravates the psychic component to such a degree that a vicious cycle is instituted, the symptoms of which are manifold These symptoms increase the severity of the emotional tension, and, if they are prolonged, permanent structural change with the production of organic disease results

The mechanism is at first a repetition of attacks, from the stimulation by an emotion such as fear upon the sympathetic nervous system, which in turn becomes increasingly labile The mechanism is perpetuated by the effects of the stimulus on the system of self-defense, which is dispatched by the endocrine group This reaction causes a state of hyperirritability to exist through the presence of tissue alkalosis, tissue hydremia, and tissue anoxemia, and results in a state of tetany which may be regional or generalized

The symptoms of tetany, and allied manifestations such as tachycardia, distended stomach and dilated urinary bladder, are enough to aggravate the neurosis because of the patient's fear of impending dissolution Multiplication of impulses increases the bombardment of the sympathetic nervous system, making repetition of the reaction more easy at subsequent intervals

The cure is accomplished through elimination of the fear-impulse by psychotherapy The symptoms may be alleviated medically, and by this means that part of the neurosis which is on the basis of anxiety concerning health may be eliminated Because of the subjective and objective improve-

ment in the patient's condition, contact for psychotherapy is more easily obtained. Medical treatment is directed toward preservation of the acid-base balance, toward decreasing the effect of adrenalin on the nerve-tissue by means of a known chemical antagonist, or toward converting the state of tone of the individual from extreme to moderate, whether parasympathetic or sympathetic in type.

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RECTAL STENOSIS FROM ROENTGEN THERAPY REPORT OF TWO CASES²

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THE simultaneous occurrence under my immediate observation of rectal stenosis following roentgen therapy in two patients with carcinoma of the prostate has served to emphasize a significant hazard in the radiation treatment of various pelvic lesions. The complication apparently is well recognized by gynecologists, proctologists and radiologists, but internists generally have not fully appreciated its frequency or clinical importance. In one of the cases which I shall report a colostomy was required and in the other, it was under consideration when uremia, as a result of bilateral ureteral obstruction from secondary carcinomatous involvement, supervened and caused the patient's death. In each of them a diagnosis of rectal irritation from roentgen exposure was made early in the course of the therapy and in each, ultimately at autopsy, an intense fibrosis of the rectal wall with narrowing of the lumen was demonstrated.

An important report on the type of the rectal lesion produced by radiation and on its symptoms and diagnosis has recently been presented from this hospital by Ferguson¹. He has also reviewed the literature and given certain clinical and laboratory data on eight cases personally studied: six irradiated for carcinoma of the cervix, one, for carcinoma of the urinary bladder, and one, for carcinoma of the prostate. I wish somewhat more fully to trace the development of the lesion in my two cases and to emphasize its relation to undesirable radiation effects in other parts of the body.

CASE REPORTS

Case 1† M J G, a physician of 72 years, who had first consulted me 17 years previously because of a transient attack of kidney colic, due to the passage of a small calculus, and subsequently from time to time for minor arthritic symptoms, complained in August 1934, of bladder irritation. He was able to void only 35 c c of urine at a time. I found his prostate enlarged and indurated. Three competent urologists‡ considered that the left lobe contained a malignant lesion and that the case was inoperable. Roentgenological study of the bones was negative for metastases. Roentgen therapy was decided upon.

The first series of treatments§ was begun on August 22, 1934 (see table 1 for details of total roentgen therapy). On October 30, one of the urologists (Pelouze)

* Received for publication August 16, 1937.

From the Gastro-Intestinal Section of the Medical Clinic, Hospital of the University of Pennsylvania.

† Included in Ferguson's series of 8 cases.

‡ Dr P S Pelouze, Dr S W Moorhead and Dr Alexander Randall.

§ The roentgen therapy in these cases was given by Dr E P Pendergrass and Dr G W Chamberlin of the Radiology Department of this Hospital.

TABLE I
Details of Roentgen Therapy in Cases 1 and 2 *
(Data submitted by Radiology Department)

Date	Portals	Dosage	
		Each	Total
Case 1		r	r
Aug 22-Sept 19, 1934	2 anterior pelvic	1845	3690
	2 posterior "	1845	3690
			7380
Nov 19-Dec 21, 1934	2 anterior pelvic	2000	4000
	2 posterior "	2000	4000
			8000
May 13-June 17, 1935	1 posterior pelvic	2025	2025
	1 perineal	1350	1350
			3375
Dec 12-Jan 17, 1936	2 anterior pelvic	2000	4000
	2 gluteal	2000	4000
			8000
Case 2		r	r
May 22-June 15, 1935	2 anterior pelvic	2000	4000
	2 posterior "	2000	4000
	1 perineal	800	800
			8800
Oct 31-Dec 4, 1935	2 anterior pelvic	2000	4000
	2 posterior "	1838	3676
	2 gluteal	1000	2000
	1 perineal	2000	2000
			11676

* Irradiation factors 165 K V , constant potential, 15 ma , 50 cm distance, 2 mm Cu or Thoreus filter equivalent to 2 mm Cu All measurements are as in air

reported marked diminution in the size of the prostate but persistent induration, by that time the patient was passing as much as 110 c c of urine at a time Toward the end of the second series of treatments he developed, in addition to subcutaneous edema of the lower abdomen, some diarrhea and bladder irritation, recognized as due to the radiation, but the latter phenomena soon subsided and his urinary output at a single voiding amounted to 260 c c His urologist then reported that the gland was little above normal in size and that the mass, previously felt in the left lobe, had disappeared He stated, furthermore, that had he not seen the patient before he could not then have diagnosed the presence of a malignant lesion

Soon after the third series of treatments (given May to June, 1935) he began to pass mucus by bowel and to have much rectal irritation On October 8, a barium enema study showed marked narrowing of the lumen of the rectum, sigmoid and descending colon Cystoscopic investigation showed an elongated posterior urethra

with a definitely raised bladder neck and 175 c c of residual urine, the prostate itself still was not very large. A trans-urethral resection by Dr Randall was done on October 18, after which he again became asymptomatic and was able to go back to his work. On December 10, his residual urine was only 10 c c.

Subsequent to the fourth and final series (given December 1935 to January 1936) he seemed in excellent general condition, and on March 14, Dr Randall reported that his prostate showed only a little deep induration and some slight fixation. On June 20, he again reported on the prostate as follows: "flat, much softer than heretofore, rather finely nodular and not sensitive, residual urine 30 c c."

In August, however, he complained of marked rectal pain, tenderness and bleeding, with bouts of constipation and spasmodic pain on attempts at defecation, for which I referred him to a proctologist (L. K. Ferguson). He found marked edema and hypertrophy of the wall of the rectum and capillary bleeding from the mucosa on the slightest trauma, effects which he unhesitatingly attributed to the irradiation.

With astringent applications and a non-residue diet the rectal symptoms subsided, but during September another trans-urethral prostatic resection was necessary. Again he returned to his work and felt reasonably comfortable, but by December 1, he had developed additional edema and marked capillary dilatations of the lower abdominal wall and had some incontinence of urine alternating with retention which required catheterization. At the same time his stools were beginning to be of small caliber and ribbon-like, sometimes he had fecal incontinence. I found, on digital examination, an annular mass in the rectum with marked constriction of the lumen, which I at first thought was due to a malignant rectal lesion. By December 28, however, the rectal wall was less indurated and a finger could pass through it, as though the stenosis were due merely to edema of the wall.

In spite of this, on January 4, 1937, Dr Randall reported improvement in his local condition with "softening of the prostate and surrounding tissues, no fixation or stony hardness, residual of 30 c c."

On March 10, he complained of a feeling of obstruction in the rectum and was unable to secure even a small liquid evacuation without a strong laxative. He was moderately anemic and emaciated in appearance, though his weight, because of the edema about the lower abdomen and back, was as usual. Again a rectal mass was palpable, but the proctoscope revealed only edema.

On April 3, he was admitted to the hospital because of marked abdominal pain and distention, fever and inability to evacuate the bowel. Rectal obstruction, due to edema and fibrosis of the bowel wall from radiation, was diagnosed. A catheter, however, could be passed slowly through the constricted area of the rectum, but only a small amount of fecal material could be washed out. Intubation of the small bowel from above allowed the escape of much gas and fluid with relief of the distention. A large mass was then felt in the right kidney area. A colostomy was considered, but he promptly became anuric, his urea nitrogen concentration rose to 140 mg per cent and he died April 7, 1937.

Autopsy revealed a primary carcinoma of the prostate with secondary involvement of the urinary bladder, chiefly about the trigone and the ureteral orifices, and bilateral pyonephrosis. The rectum itself was not involved in the malignant process, but, according to the pathologist (O. N. Smith) "in the rectum, beginning about 3 cm from the anal orifice and extending proximally for about 12 cm, there was a brawny thickening of the wall, most conspicuously involving the muscularis and simulating the hypertrophic changes seen in pyloric stenosis. This markedly constricted the caliber of the lumen, so that the index finger could be passed only with considerable force. Although the rectum was adherent to the posterior surface of the bladder, the diffuse involvement of its wall was not grossly neoplastic." Dr Morton McCutcheon reported on his microscopic study of the sections as follows:

"There is marked chronic proctitis, characterized by mucosal destruction and by submucosal edema, fibrosis and inflammatory exudate. The inner muscularis is markedly degenerated, vacuolated with fat, and conspicuously replaced by fibrous tissue. Several arterioles are markedly hyalinized. The outer muscularis is less damaged. The fibrosis and muscular degeneration are much more marked in the rectum than in other sections of the sigmoid, small intestine and stomach."

COMMENT ON CASE 1

It will be noted that following the second series of treatments, and about four months after the beginning of radiation, diarrhea was first observed. Following the third series, five months later, he was passing much mucus by rectum and about one year after the first radiation a barium enema showed marked narrowing of the lumen of the rectum, sigmoid and descending colon. Again, however, he became asymptomatic, and in spite of the necessity for a prostatic resection (to relieve bladder retention) and a fourth series of roentgen treatments, he had no further significant rectal symptoms until August 1936, two years after the first treatment. Then he was proctoscoped for the first time and the examination disclosed rectal edema, hypertrophy of the wall and capillary bleeding. In spite of these local phenomena his rectal symptoms again subsided temporarily, but four months later he became constipated, had spasms of pain on defecation and the stools, when formed, were ribbon-like in character. Digital examination showed marked narrowing but the finger could be introduced slowly, apparently as the edema was reduced by pressure. This observation was subsequently confirmed by the proctoscope. Autopsy four months later, however, showed not only edema but true fibrosis of the wall.

Thus it seems clear that, although early he developed some irritation of the rectal wall, it was transient as also was some of the edema that occurred later, and not until after almost two and a half years did he develop the true fibrous and stenotic lesion which was found at autopsy.

Case 2 E. M., male, 72 years of age, a business man with large responsibilities, was referred to me by Dr. Isaac W. Kingsbury, of Hartford, Conn., on March 8, 1935, complaining of epigastric discomfort, relieved by alkalies, and of attacks of substernal distress with reference into the left arm after physical and mental strain. He was of the tall, thin, duodenal ulcer type, obviously arteriosclerotic, had systolic murmurs at the apex and base of his heart but no enlargement, and a blood pressure of 130 systolic, 85 diastolic. His prostate was moderately enlarged and firm. Urine, blood and stool examinations were negative. Free hydrochloric acid was present in excess in his gastric contents. An electrocardiogram showed some extrasystoles and evidence of myocardial damage. Gastrointestinal roentgenological study revealed a large active duodenal ulcer.

On May 17, 1935, Dr. Alexander Randall found characteristic evidence of prostatic malignancy. Roentgen study of the bones showed no metastases. Roentgen therapy was started at once (table 1). After the first series of treatments the prostate was much improved—smaller, more elastic and less nodular. Meanwhile he had developed some nausea and vomiting and had lost some weight (from 169 to 160 pounds). His ulcer symptoms had subsided and he had no more disturbing cardiac

attacks. Subsequently (July) some irritation of the skin in the hypogastrium developed and he had some frequency of bowel evacuations and irritability of the urinary bladder. On July 12, another gastrointestinal roentgen study showed the duodenal ulcer defect still present but associated with less spasm.

He had regained his usual weight by October and was in good general condition, but the left lobe of the prostate was larger and firmer. A second series of roentgen treatments was begun, and in the midst of that he developed marked edema and irritation of the lower abdominal wall, the buttocks and the perineal region. On completion of the series, however, the prostate seemed smaller and less hard. Again he had lost weight but, except for the skin lesions, one of which had ulcerated, was in good shape. Some fecal incontinence developed a few weeks later and the urinary bladder again became very irritable.

By January 27, 1936, he had regained his weight and the skin condition had improved though some hard edema persisted. He was able to go through the night without voiding.

On his return, in April, from a trip to the west coast, where he played as much as 12 holes of golf without incident, he had no special complaints, but his prostate was a little larger and seemed fixed to the bone on the left side. A month later he had some leg pains, suggestive of bone metastasis, but roentgenological examination was negative. On the basis of special vascular tests it finally was decided that the pains were on an arteriosclerotic basis and some "suction and pressure" therapy was given.

Prostatic examination by Dr. Randall, on September 24, revealed no new developments, but again he was having marked bladder irritation with nocturnal frequency. Shortly afterwards he developed a recurrence of the fecal incontinence. On November 25, he was complaining of stiffness in the loins and above the iliac crests but no abdominal masses could be felt. Edema of the groins and perineum was still marked. On December 18, he developed suddenly left chest pain and hemoptysis which suggested a pulmonary infarction, but roentgen study of the lungs showed only thickened trunk shadows, and he had subsequently no recurrence of the pain or hemoptysis. At the same time he developed some pain in the lower abdomen and back, but it was not persistent.

On April 17, 1937, he was complaining particularly of fecal incontinence, especially on urinating, alternating with constipation for 3 or 4 days. Blood frequently appeared in his stools. His appetite was impaired and he was losing weight (152 pounds). His sigmoid was full and doughy. On rectal examination marked edema of the wall with narrowing of the lumen as far as one could reach was found, and above that a mass in the lumen, probably fecal. Anteriorly through the edematous wall marked induration could be detected and a spreading prostatic lesion was suspected.

A week later he was again referred to the hospital because of abdominal pain, failure to evacuate the bowel and a suspicion of intestinal obstruction. The lower abdomen was tense and sore. Digital examination of the rectum showed diffuse induration but a smooth wall. A finger could barely be inserted. Finally a urethral catheter was slowly passed for 10 to 12 inches into the lower bowel and through that much blood and fecal material were evacuated, as a result of which he became quite comfortable. That procedure was repeated several times, but finally the results were unsatisfactory, and on April 30, a colostomy was performed by Dr. E. L. Elrson. The patient was quite alert after the operation for two hours, but then rather suddenly became distressed, cyanosed and dyspneic, developed a leaky skin and feeble pulse and died.

Autopsy by Dr. O. N. Smith showed that death had resulted from complete occlusion of the left coronary artery, already extensively sclerosed and calcified.

The prostate was only slightly enlarged and without induration suggestive grossly of carcinoma, but in the left lobe was a mass of gray tissue, 1 cm in diameter, which microscopic study showed to be malignant. The rectum was markedly compressed by a mass of carcinomatous tissue which lay between it and the sacrum. The urinary bladder and ureters were not involved, but the lymph nodes along the abdominal aorta, about the head of the pancreas and those situated extraperitoneally in the pelvis were massively implicated. The sigmoid was adherent to the peritoneum below the pelvic brim and the upper rectum was more or less encased in carcinomatous tissue. The rectal mucosa, however, was not carcinomatous, but it was infiltrated with round cells and polymorphonuclears. The submucosa was edematous and fibrotic. The muscular cells were vacuolated and degenerated. The perimuscular adipose structure was infiltrated with fibrous tissue and edematous, and it contained an occasional metastatic carcinomatous mass, the result of lymphatic spread. The lungs showed metastatic lesions. The duodenum showed a small healed ulcer and the liver, multiple cysts, one of which contained 600 c c of fluid.

COMMENT ON CASE 2

The obstruction in this case obviously was due in part to the metastases which surrounded the rectum, but also in part to the edema and fibrosis of the rectal wall. The fact that a finger could be inserted into the lower rectum only very slowly, seemingly displacing fluid from the wall as it passed, and that a semi-rigid rubber tube could be introduced only in the same way left no doubt in the mind of the examiner that he was dealing with stenosis due to edema. The observations at autopsy, furthermore, indicated that the compression of the rectum by the metastatic lesions was not sufficient in itself to produce complete obstruction.

In this case also it will be noted that irritation of the rectum, indicated by diarrhea, occurred soon, about two months, after beginning radiation therapy, but was transient. Fecal incontinence came on after the second course of treatment, but that also subsided within a short time. It recurred, along with bladder irritation, however, after another year and then persisted until he developed definitely obstructive symptoms. Unfortunately no proctoscopic study was made in this case, but the frequent presence of blood in the stools suggests that, in addition to edema of the wall, telangiectatic areas, such as have frequently been demonstrated in other cases, were present.

GENERAL DISCUSSION

The intimate anatomical relationship of the rectum to the urinary bladder, the prostate and the cervix of the uterus accounts for its involvement when any of these organs is subjected to intensive radiation therapy. Although the portal of entry of the roentgen-rays through the skin may be altered from time to time, it is impossible to direct the rays so as to avoid almost maximal exposure of the deeper tissues in the immediate neighborhood of the lesion under treatment. The skin reaction, therefore, cannot be a measure of the effect produced internally on adjacent structures.

That intensive radiation is capable of producing irritating and eventually destructive effects elsewhere in the digestive tract is well ap-

preciated Desjardins² has reviewed the literature in reference to its action in the mouth, where in overdosage it produces ulcerative lesions, permanent telangiectases and serious dental disturbances, to its destructive action on the salivary glands, to the degeneration of epithelium, hyperemia, hemorrhage, atrophy and fibrosis which occur in the stomach, and to the mucoid degeneration, hyperemia, edema, ulceration and fibrous tissue replacement that take place in the small intestine Nelson and Hirsch,³ in reporting a case treated for suspected malignancy of a cervical lymph gland, state that the autopsy showed severe necrosis and scarring of the pharynx, larynx and upper parts of the trachea and esophagus Schenck⁴ has repeatedly observed irritation and edema of the larynx in patients given roentgen therapy for hyperthyroidism Elliott and Jenkinson⁵ had a patient who died as a result of intestinal perforation secondary to ulceration from roentgen therapy for abdominal Hodgkin's disease

Irritation of the urinary bladder, such as occurred in both of my cases, has been more often reported as a result of radium treatment for carcinoma of the cervix, but roentgen therapy also has been employed in most of these cases Everett⁶ refers to 18 cases, so treated, 7 of whom eventually developed a vesico-vaginal fistula and 11, bilateral ureteral stricture Dean⁷ has studied 47 women for lesions of the bladder incident to radiation therapy cystoscopic investigation, on an average of two and a half years after the therapy, showed ulceration and anemic areas surrounded by intense inflammation or punctate hemorrhage He stated that these lesions might follow comparatively light applications of irradiation

The incidence of rectal complications of radiation therapy is indicated by Bue and Malmgren's⁸ statement that in 2,073 cases subjected to pelvic irradiation for extra-rectal lesions they found 3.13 per cent that had rectal symptoms and a lesion discoverable by the proctoscope The onset averaged 11.6 months after treatment and the outstanding symptoms were bleeding, pain, diarrhea, urgency and tenesmus The proctoscope invariably showed telangiectases and bleeding Ulcers were present in 43 per cent of the cases

In a series of 520 cases of cervical carcinoma treated by irradiation eight months to eight years previously, Jones⁹ found seven instances of benign stricture of the intestine, although none of them had received excessive dosage according to present standards Only one had the stricture in the rectum, but five in the sigmoid The lesion in all instances was an annular fibrous thickening, localized and obstructing the bowel Newell and Crossen,¹⁰ in a series of 371 irradiation cases, had five with rectal stricture, but all were of slight degree and satisfactorily treated by dilatation

Jones,¹¹ Ferguson¹ and other authors have recognized early and late phases of the rectal reaction to radiation the one occurring within a few weeks or months after treatment, the other, months or years later Jones, whose observations were made on women with cervical carcinoma who received radium, stated that a dose sufficient to cure the lesion would produce erythema of the rectum and that the early symptoms of the latter were a

burning sensation and frequency of defecation, while later, after six to eight months, in the more severe cases, marked pain and tenesmus with blood and mucus might develop. Ferguson, whose experience has included patients treated not only with radium but also only with the roentgen-ray emphasizes the severity of the early symptoms chiefly in the radium cases. This seems reasonable since they receive a larger dosage of irradiation at one time. In neither of my cases was anything more than a slight and transient diarrhea, with the occasional passage of mucus, noted in the first phase of the reaction. In spite of this, both eventually, after an interval of freedom, developed the characteristic late symptoms: spasms of pain on attempt at defecation, diarrhea alternating with constipation, marked tenesmus and bleeding with and after each bowel movement. On two occasions in one of the cases a proctoscopic examination, made late in the course of the illness, revealed a contracted, edematous and bleeding rectal wall. The other case was not proctoscoped, but in both, the autopsy findings demonstrated clearly the presence of marked edema and fibrosis producing stenosis. Telangiectases were not observed, but since they have frequently been described in such cases it is to be assumed that they were present and accounted for the bleeding.

CONCLUSION

Two cases of stenosis of the rectum, due to intensive radiation therapy for carcinoma of the prostate, are presented in order to call attention to its occurrence. Although in each of these cases the malignant lesion had not been eradicated by the radiation and early death was inevitable, it is believed that the recognition of such rectal stenosis in certain other patients, in whom the primary lesion is under control, may lead to appropriate surgical therapy and be life saving.

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PANCREATITIS AND DIABETES *

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THE involvement of the pancreas as a cause for diabetes is, to a great extent, taken for granted. The exact changes in the pancreas responsible for the development of diabetes are not clearly defined. The situation is a good deal as though all pulmonary conditions—tuberculosis, the pneumonias, abscess, bronchiectasis, asthma, passive congestion—were classified as a disease entity characterized by expectoration and all treated alike on that basis.

Certain phases of pancreatic pathology—carcinoma, cyst, adenoma—are well established, but the lesions resulting in diabetes are not satisfactorily evaluated. An attempt will be made in this paper to correlate the changes in the pancreas with the various manifestations characteristic of diabetes. The gradual development of knowledge in regard to the anatomical and the functional pathology of the pancreas warrants an effort of this sort at the present time, though the conclusions reached are tentative only and await further clinical and laboratory data for their elaboration.

PATHOLOGY OF THE PANCREAS IN DIABETES

An involvement of the majority of the islands of Langerhans causes diabetes, the pancreatitis resulting in such lesions may be chronic or acute, permanent or transient.

CHRONIC PANCREATITIS

Chronic pancreatitis develops in elderly persons because of arteriosclerosis and senescent processes. This form of chronic pancreatitis may be regarded as primary chronic pancreatitis. When the chronic pancreatitis is the sequel, through scarring, resulting from an acute pancreatitis or from pancreatic duct obstruction, it may be considered as secondary chronic pancreatitis.

PRIMARY CHRONIC PANCREATITIS

This type of pancreatitis results in the slowly progressive form of diabetes which occurs in late middle life and in old age, it is generally known as the essential diabetes of Naunyn, and should be ascribed to the degenerative changes incident to advancing years. It should be sharply distinguished

* Received for publication September 15, 1937.

Acknowledgment is made to Dr. S. H. Schechner for the reference of Case 4, to Dr. R. F. Carter for the operative findings, and to Dr. M. Bruger for many of the data on the same patient.

from the forms of diabetes characterized by exacerbations and found in younger individuals

Warren calls attention to the occurrence of three predominating lesions in the islands of Langerhans in his series of 259 diabetic pancreases, as follows

Total Number of Cases—259	
Normal	69
Fibrosis	69
Hyaline	89
Hydropic degeneration	15

The above tabulation furnishes data only in regard to the qualitative changes in the islands of Langerhans and gives no information about a diminution in their number. It may very well be that in the group designated as normal, a number of islands have disappeared and left no trace which can be identified under the microscope.

Hyalinization of the islands of Langerhans occurs almost entirely in persons over 40 years of age, it is also found in non-diabetics. Fibrosis, like hyalinization, is more frequent in older individuals and yet, though common, is not often mentioned as a cause for diabetes. Joslin subscribes to the idea that fibrosis of the islands is nearly as common a finding as hyalinization. Fibrosis and hyalinization of the islands may appear in the same pancreas and the two lesions may even be combined in the same island. It is tempting to assume that both fibrosis and hyalinization of the islands are part of the aging process and the arteriosclerosis incident to human existence.

SECONDARY CHRONIC PANCREATITIS

Secondary chronic pancreatitis results from destruction of the pancreas brought about by obstruction of the pancreatic ducts, through pancreatic calculi or external pressure, by acute pancreatitis, and by pancreatic cysts or hemorrhage within the pancreatic tissue. The subsequent development of diabetes depends upon the number of islands of Langerhans which are destroyed. Very frequently, probably in most cases, too few islands are involved to result in diabetes. Especially noteworthy in this connection is the experimental observation of MacCallum that after ligation of a pancreatic duct, all the corresponding pancreatic tissue atrophies, except the islands of Langerhans, which are preserved, this has been verified in human beings with long standing obstruction of the pancreatic ducts.

The diabetes resulting from secondary chronic pancreatitis is usually mild and non-progressive (see Case 5) unless there is a recurrence of the process which extends the involvement of the islands of Langerhans.

ACUTE PANCREATITIS

Fitz in 1889 designated the varieties of acute pancreatitis as hemorrhagic, gangrenous and suppurative, while these three types of injury are

still recognized they have come to be regarded as parts of the same process, that is acute pancreatitis (Pratt, Warfield, MacCallum and others) Pratt says "The subdivisions made by Fitz into hemorrhagic, gangrenous and suppurative forms of acute pancreatitis represent different stages in the same pathological process which begins with necrosis of the pancreas" This severe form of acute pancreatitis, characterized clinically by marked epigastric pain, shock and collapse, was the only one recognized for a long time and is the only one considered by many clinicians today

Pratt was one of the first to describe the mild cases, differing largely from the severe cases in that a smaller amount of pancreatic tissue was involved Since then, Warfield, Dragstedt, Haymond and Ellis, and Rich and Duff, have made the same observation Such minor involvements of the pancreas according to all these observers are frequently found The turbulent course of diabetes in the young is probably due to recurring attacks of this sort The rarity of acute pancreatitis, as stressed by Root, would consequently apply only to the severe form and not to the milder, non-fatal attacks

The etiology of acute pancreatitis has been a matter of considerable debate The majority of authors specify diseases of the gall-bladder as being primarily responsible Dragstedt, Haymond and Ellis, in an intensive study of this problem, come to some very important conclusions Edema and hemorrhage of the pancreatic parenchyma are frequent findings, they constitute milder attacks of pancreatitis, which may develop into necrosis, limited or extensive, that is, the significant change of severe acute pancreatitis These authors believe that bile, and infection by *B welchii* are the separate determining factors in bringing about the necrotic process (This is in contrast to the opinion of others, e g, Rich and Duff quoted subsequently)

According to Dragstedt, Haymond and Ellis, it is probable that approximately 60 per cent of the cases of acute pancreatitis in man have developed as a direct result of the passage of bile into the pancreatic ducts, the causes of the pancreatitis in the remaining 40 per cent are (1) extension of infection via the lymphatics from an infected gall-bladder or neighboring viscus, (2) trauma, (3) hematogenous infection, as in mumps, (4) stasis of the pancreatic juice—plus infection, (5) reflux of the duodenal contents into the pancreas

Rich and Duff, from their experimental and pathological studies, develop the idea that the main cause for acute pancreatitis is occlusion of the pancreatic ducts, the stoppage may be brought about by gall stones lodged in the papilla of Vater, or as they stress, by metaplasia of the epithelium of the branches of the pancreatic duct The latter condition was found to exist in 18.6 per cent of autopsies in individuals over 25 years of age They believe, in contrast to Dragstedt and his co-workers, that because of the obstruction trypsin and steapsin are liberated and result in necrosis of the

arteries, producing hemorrhage, necrosis of other elements in the pancreatic tissue, and in fat necroses

The clinical manifestations resulting from chronic or acute pancreatitis are of three varieties, each caused by the involvement of a specific element in the pancreatic tissue. One or the other of these impairments may be present singly or they may co-exist. These symptom complexes will be discussed under the heads

- 1 Carbohydrate metabolism
- 2 Fat metabolism
- 3 Blockage of the pancreatic ducts

CARBOHYDRATE METABOLISM AND THE PANCREAS

Chronic pancreatitis, due to arteriosclerotic and senescent lesions in the islands of Langerhans, is accepted as being the cause of the mild, slowly progressive diabetes of older persons. This form of diabetes was called essential diabetes by Naunyn and is still known by that name.

In younger individuals, diabetes pursues a much more irregular course, punctuated by periods of marked loss in carbohydrate tolerance. Wilder (quoted by Warfield), and Warfield have suggested that repeated attacks of mild acute pancreatitis, followed by some permanent injury to the islands of Langerhans, might be the reason for this type of diabetes. Case 1 (table 1) is an example of this sort.

CASE REPORT

Case 1 S R, student, male, in September 1933, at age 18, developed a glycosuria, he had been 14 lbs overweight, complete physical examination, except for glycosuria and hyperglycemia, was negative in all respects.

The details of the course of the diabetes are shown in table 1.

In any case of acute pancreatitis the degree to which the carbohydrate metabolism is implicated will depend upon the number of the islands of Langerhans that are involved so that an acute pancreatitis may or may not be accompanied by hyperglycemia and glycosuria, an acute pancreatitis may result in diabetes (Case 6), it may bring about no change in the severity of an existing diabetes (Case 5), it may aggravate a diabetes permanently (Case 1), or it may cause the transient appearance of diabetes which subsequently clears up (Case 4).

The oxidation of fat is in part associated with the carbohydrate metabolism. It is an old and accepted principle in the metabolism of diabetes, formulated by Magnus Levy, that "The fats burn in the fire of the carbohydrates." This does not mean that the oxidation of fats depends entirely on the utilization of glucose but only that the oxidation of B-oxybutyric acid is contingent upon the carbohydrate metabolism. The change from the fatty acids of a chain of 16 or 18 carbon atoms, that go to make up

TABLE I

Date	Urine Glucose %		Insulin * Units per Day		Changes in Glucose Tolerance
	p m	a m	Individual Dose	Total	
1933 Oct 16	0 0	-0 0	10-10	20	<i>Acute onset of diabetes five weeks before</i>
1934 May 8	0 0	0 0	12-8	20	<i>No change in glucose tolerance during six months</i>
July 24	2 1	2 0	* 12-10	22	<i>Exacerbation of diabetes, abscessed tooth and "swollen jaw" early in July</i>
Aug 21	0 0	0 0	16-8-12-8	44	
Oct 30	0 0	0 0	18-10-10-10	48	<i>Gradual diminution of glucose tolerance for 14 months</i>
1935 May 23	0 0	0 0	20-10-10-14	54	
Aug 29	0 0	0 0	24-10-12-14	60	
Nov 13	0 0	0 0	26-10-12-16	64	
1936 Jan 20	0 0	0 0	26-10-12-16	64	<i>No change in glucose tolerance for 14 months</i>
Sept 9	0 0	0 0	26-12-12-16	66	
Dec 3	0 0	0 0	20-10-20-10	60	
Dec 29	0 0	0 0	50, 10	60	
1937 Jan 19	1 5	2 0	35-35	70	<i>Exacerbation of diabetes, with partial recovery of sugar tolerance The only cause to which this and the two subsequent exacerbations can be attributed is the nervous strain of taking examinations and entering upon the career of accountant by an ambitious young man</i>
Feb 23	0 0	0 0	40, 15-40, 15	110	
Apr 13	0 0	0 0	40-30	70	
Apr 24	0 0	0 0	80	80	
May 22	2 5	2 4	80	80	<i>Exacerbation of diabetes</i>
June 30	0 0	0 0	50-50	100	
July 29	1 2	1 3	50-50	100	<i>Exacerbation of diabetes</i>

Table 1 Case 1 Four year history of the changes in the loss of sugar tolerance in a diabetic aged 18 years, at the onset of the diabetes While there have been no signs or symptoms of pancreatitis other than glycosuria, it is suggested that comparatively mild, recurring attacks of pancreatitis are responsible for the irregular progress of the disease

* Plain figures show regular insulin, italicized figures protamine, or protamine zinc insulin, the individual doses of insulin are separated by a dash

neutral fats, to the 4 carbon chain of B-oxybutyric acid is governed by other agencies An excess of B-oxybutyric acid results in diabetic acidosis and coma A markedly impaired carbohydrate metabolism, therefore, will be associated with acidosis and coma, but the oxidation of fats to the stage of B-oxybutyric acid does not depend upon the islands of Langerhans and their influence upon glucose oxidation Another part of the pancreas controls the transport and utilization of fat up to the point of B-oxybutyric acid formation The significance and symptomatology of this pancreatic function will be discussed in the next section on fat metabolism

FAT METABOLISM AND THE PANCREAS

Previous mention has been made of the fact that the complete oxidation of fatty acids and the prevention of acidosis depends upon the proper utilization of glucose. A closer study of cases of diabetes reveals the fact that the disposition of fat is a pancreatic function entirely apart from that of carbohydrate utilization or that of absorption of fats from the intestinal tract. The signs and symptoms of deficient fat metabolism noted in diabetes are

Hypercholesterinemia
Lipemia
Xanthoma
Fatty liver and spleen

Hypercholesterinemia occurs in some mild diabetics whose carbohydrate metabolism is well controlled and in whom there is no acidosis. The cholesterol content of the blood parallels the total fatty acids fairly well and may be taken as an index of the degree of lipemia.

Case 2 Male, aged 38, diabetes for four years, observed for more than one year. During that period no insulin was required, nine determinations of blood sugar taken after breakfast were normal, varying from 98 to 167, the blood specimens were always lipemic and the plasma cholesterol was distinctly elevated, ranging from 248 to 400. At no time was there acetone or diacetic acid in the urine. The physical examination was normal except for a large spleen which was tender and whose lower pole extended three fingers' breadth below the costal margin, the liver edge was at the costal margin.

This case was interpreted as being one of diabetes with very marked dissociation of the effects upon the carbohydrate and the fat metabolism. The distinct disturbance of the fat metabolism was evident from the persistent lipemia, the high plasma cholesterol and presumably fat deposits in the spleen, while the carbohydrate metabolism was scarcely affected, since there was only transient glycosuria, the blood sugar was nearly always at a normal level, insulin was not required and dietary restriction alone served to control the situation. The relationship between the elevated blood cholesterol and the control of blood and urine sugar in this instance, is not at all like that which is usually accepted, in that the successful management of the carbohydrate metabolism did not serve to reduce the high level of the blood cholesterol.

Another similar example of dissociated fat and carbohydrate metabolism is Case 3.

Case 3 Male, aged 57, diabetes discovered three years ago on routine urine examination, five years ago accepted on life insurance examination for a large sum. Forty pounds overweight for height and age, otherwise physical examination shows nothing of note. The interesting point in this patient lies in the fact that the plasma cholesterol was continuously high and had a tendency to rise in the face of fairly good control of the diabetes. From August 1935 to August 1937, plasma cholesterol determinations made at intervals, were as follows: 238, 200, 238, 261, 296, 312, 343, 312, 369, 278.

Lough and Killian report the case of a young male diabetic, aged 20, who after seven months' dietary indiscretion, developed xanthoma diabeticorum, lipemia and acidosis. The total fatty acids in the blood were 9,200 (normal 600) and the plasma cholesterol 1,072 (normal 180). In this patient, as in most similar instances, the xanthoma, the lipemia, the glycosuria and the acidosis all cleared up on treatment of the disturbed carbohydrate metabolism, however, here as in many other cases, there was a lag of the return to normal of the lipemia as compared to the blood sugar and the acidosis. This bears out the conception that both the carbohydrate and fat metabolism are affected by an involvement of the pancreas, yet they are not acted upon synchronously and, consequently, it is fair to assume that such changes are brought about by the suppression of a different pancreatic function.

The symptom complex of severe acute pancreatitis,—glycosuria, acidosis, rise of blood cholesterol, lipemia, xanthoma, fatty liver and spleen—often develops so precipitously as to produce a completely baffling picture that defies analysis, on the other hand, there are cases of pancreatitis recorded in which each of these symptoms appears individually and apparently independently of the others. Instances of acidosis without lipemia are common (Herbert), cases of pancreatitis with lipemia or xanthoma developing in advance of, or in the complete absence of glycosuria, are reported. These facts have led Wijnhausen (1921), Joel (1924), Brunner (1935), and Root (1936) to stress the idea that there is a specialized function of the pancreas, which checks lipemia, xanthoma, fatty liver and spleen, apart from the regulation of the carbohydrate metabolism effected by the islands of Langerhans.

A recent case of recurring pancreatitis, with an almost record level blood cholesterol and lipemia, is the following:

Case 4 Male, aged 35, first seen on April 24, 1936

History Acute appendicitis, not operated on, 1921 (in view of subsequent events this may have been an attack of acute pancreatitis). March 1935, passed a life insurance examination, September 1935, glycosuria discovered for the first time, December 1935, acute pain in the epigastrium which disappeared in a few days, April 24, 1936, a recurrence of the acute pain in the epigastrium which became so severe that operation was resorted to.

Physical Examination Markedly obese (85 lbs overweight for height and age), xanthomata were scattered over the neck, abdomen and legs. The edge of the liver was four fingers' breadth below the costal margin and the liver was distinctly tender, the spleen was not enlarged. The heart rate was 120, there was no other sign of collapse or shock, the patient walking about without embarrassment, and the blood pressure was 132 systolic and 94 diastolic. Otherwise a complete physical examination showed nothing of note.

Laboratory Observations April 24, twenty-four hours prior to the admission of the patient to the hospital, the urine sugar was 3.3 per cent and acetonuria was graded two plus. The plasma was markedly lipemic. The blood sugar was 400 mg per cent, the total plasma cholesterol 2037 mg per cent, and the total fatty acids in the plasma 1738 mg per cent. Leukocytes numbered 16,800 with 76 per cent polymorphonuclear neutrophils. April 25, on admission to the New York Post-Graduate

Hospital, the urine still showed marked glycosuria and acetonuria. The blood sugar had decreased to 214 mg per cent. The leukocytes now were 25,450 with 80 per cent polymorphonuclear neutrophils. The administration of 140 units of insulin in divided doses over a period of nine hours rendered the urine sugar and acetone free. Within 48 hours after the initiation of intensive treatment and immediately prior to the operative interference, the blood sugar had decreased to 180 mg per cent, total cholesterol to 1041 mg per cent, and the fatty acids to 394 mg per cent.

TABLE II

	Urine		Blood Sugar mg %	Plasma Chol mg %	Prota- mine Insulin Units	Orange Juice c c	
	Vol- ume c c	Sugar					
		%					gm
4/29/36							
3 30 a m	300	2 0	6 0				
6 15 a m	520	1 7	8 3				
8 00 a m			200	735	100	120	
11 00 a m			227	655		100	
11 30 a m	490	1 7	6 8				
2 00 p m			211	628		100	
5 00 p m			179	707		100	
5 30 p m	500	1 8	9 0				
8 00 p m			185	651		100	
10 00 p m			185	600		100	
12 00 p m	400	1 0	4 0			100	
Total	2210	34 1				Total carbohydrate 72 gm	
4/30/36							
8 00 a m			164	571	100	100	
9 30 a m	450	0	0			200	
11 00 a m			204	598		200	
2 00 p m			172	535		200	
5 30 p m	300	0	0			200	
8 00 p m			149	577		200	
10 00 p m			206	543		200	
Total	750					Total carbohydrate 130 gm	

Table 2 - Case 4 The findings on the second and third days post-operative in a case of acute pancreatitis, showing the effect of single large doses of protamine insulin on the urine sugar, blood sugar and plasma cholesterol. The pre-operative cholesterol figures were much higher 2037 and 1041 mg per cent.

Operative Findings On April 27, Dr R. Franklin Carter operated at the New York Post-Graduate Hospital and his operative notes were: On opening the abdomen the gall-bladder was found to be distended but not acutely inflamed. The abdomen was filled with a yellowish-green pus. When the incision was extended the appendix was found to be hanging over the brim of the pelvis and adherent at the base but not acutely inflamed. The upper abdomen was searched. Adhesions were found between the hepatic flexure and the colon and the lateral abdominal wall. The adhesions were found to be fibrotic and in the adhesions there was found to be a yellow slough behind the colon involving the fat of the colon wall. The duodenum was normal. Looking up above the duodenum along the common duct, pus was found to be exuding through

an opening in the retroperitoneal covering of the common duct and draining into the abdominal cavity. Bile in the gall-bladder was found to be very thick, tar-like in character. *Operation* cholecystostomy—drainage of the abdomen. *Diagnosis* acute destructive pancreatitis involving chiefly head of the pancreas with biliary obstruction (No fat necrosis in abdomen). General peritonitis.

Post-Operative Course complete recovery, discharged 27 days post-operative.

Fifty to 75 units of regular insulin daily in divided doses did not control the post-operative glycosuria. Protamine insulin in single doses of 100 units, buffered by moderate amounts of orange juice every few hours, proved to be more satisfactory (table 2).

The lag of the plasma cholesterol as compared to the immediate response of the blood sugar and the glycosuria, as in the case of Lough and Killian and others, is very evident (table 2). This observation is borne out by experiments on human subjects in which a single dose of insulin did not produce any significant change in the blood cholesterol even though the blood sugar changed from a distinct hyperglycemia to hypoglycemia (Bruger and Mosenthal). The distinction between fat and carbohydrate control by the pancreas is thus stressed.

The subsequent history of this case showed that there was complete recovery from the damage to the pancreas, insulin was never required, an anti-obesity diet was followed for two months with a loss of 35 lbs, but at the end of that period he again "ate everything" including starches, and after eleven months had regained all the lost weight. The interesting points here are that the carbohydrate metabolism remained normal though there was some evidence of disturbance in the fat metabolism, the urine remained sugar free, the blood sugar, taken after breakfast, was 93 mg and 111 mg per 100 c c, and no insulin has been used, the plasma cholesterol values on the other hand were somewhat elevated being 256 and 343 mg per 100 c c. Uncomplicated obesity, as shown by Bruger and Poindexter, is characterized by a normal level of plasma cholesterol, the high figures here would consequently point to an involvement of the fat regulating structures of the pancreas, whereas the islands of Langerhans controlling sugar utilization had made a complete functional recovery. The independence of the influences of the pancreas upon the fats and the carbohydrates is again emphasized.

The tenderness of the liver in this case and the tenderness of the spleen in Case 2 are noteworthy. It may be that deposition of large quantities of fat in the liver and spleen may result in tenderness and this may prove to be a sign of diagnostic value.

The solution of the problem of the existence of a disturbance in fat metabolism through the pancreas, apart from that regulating the carbohydrate metabolism, may be provided by the discovery of the hormone "lipocain" by Dragstedt, Van Prohaska and Harms. In their own words this material is described as follows: "a specific substance has been obtained in alcoholic extracts of beef pancreas, that on oral administration to depancreatized dogs treated with insulin, permits survival and prevents and relieves the fatty degeneration and infiltration of the liver of these animals. This substance, for which the name 'lipocain' is suggested, is believed to be a new

hormone that is concerned in some way with the normal transport and utilization of fat "

The "lipocaic" awaits clinical trial. It is sincerely hoped that it will prove successful in controlling the hypemia and hypercholesterinemia, so common in diabetes, and the more severe, though less frequent, disturbances—the fatty liver and spleen, and xanthomata. If the thesis proposed here and by others, that there is an independent control of fat and carbohydrate metabolism by the pancreas, is correct, then it would be expected that "lipocaic" should set aside the derangement of the fat metabolism in diabetes, and it might be particularly valuable in preventing the dreaded vascular complications of the disease.

BLOCKAGE OF THE PANCREATIC DUCTS

The pathognomonic sign of occlusion of the pancreatic ducts is the occurrence of "pancreatic stools", the typical pancreatic stools are soft, very voluminous in shape, size and consistency, when passed into a bed pan they resemble those of cattle, they are yellowish and glistening (due to the presence of free fat), they are malodorous (due to putrefaction, since the proteins are hemmed in by free fat which permits the growth of anaerobic organisms, but prevents the digestion and absorption of meat, etc.), there are usually from three to six of such bulky movements a day, the laboratory tests of these excreta are not as reliable as the macroscopic appearance just mentioned, free fat and undigested meat fibers should be seen on microscopic examination. There should be an absence of pancreatic ferment, the lack of which can be more reliably demonstrated by examination of the duodenal contents.

The signs of diabetes may precede the appearance of the pancreatic stools (Case 5), or may appear after the closure of the pancreatic ducts has become manifest (Case 6). There are many instances in which occlusion of the pancreatic ducts is not accompanied by diabetes as might be expected according to MacCallum's findings, previously mentioned, that uncomplicated blockage of the pancreatic ducts results in atrophy and sclerosis of the acinar tissue, while the islands of Langerhans are preserved. Whether an existing diabetes remains unchanged or undergoes an exacerbation with stoppage of the pancreatic intestinal secretion depends upon the presence or absence of pancreatitis and the involvement of the pancreatic ducts in diabetics. (Case 6 is abstracted from a previous publication, Mosenthal, 1912.)

Case 5 Male, first seen 12 years ago (1925) when he was 55 years old. There was then a mild diabetes which was readily controlled by diet. Progress was uneventful until October 1928 when there was some vague discomfort in the epigastrium. Two series of roentgen-ray films revealed no definite lesion. During April and May 1929, there was a series of chills and fever about once a week, the chills were severe and were followed by rises in temperature up to 104 and even 105 degrees. At this time typical "pancreatic stools" appeared. During the eight following years the

number and size of the stools could be checked only by the feeding of raw pancreas. The diabetes was not aggravated by the fever and has remained unchanged during the eight ensuing years.

*Case 6** Male, aged 20. During the latter part of November 1909, he had an attack of intense abdominal pain without diarrhea or fever, one month later a marked glycosuria was found, in January 1910 he had frequent attacks of vomiting accompanied by a "burning sensation" but no frank abdominal pain in February the vomiting ceased, the stools however at this time changed in character, became large and putty-like and were said to resemble "mavonnaise" the stools have continued unchanged up to the present (May 1910). The results of pancreatic medication are given in table 3.

TABLE III
Urine in Twenty-Four Hours

Date, 1910	Glucose gm	Total N gm	Ammonia gm	Ammonia N as Per Cent of Total N	Total Acid Substances as B-oxy-butyric Acid gm	Number of Stools per Day	Medication
May 11	137.5	17.5	2.8	13.3	5.3	3	"Pankreon" 0.5 gm three times a day, May 11-19
May 12	88.0	—	0.3	—	—	1	
May 13	94.7	20.7	1.9	7.7	4.9	4	
May 16	95.2	—	1.6	—	—	2	Raw sheep's pancreas 50 gm three times a day, May 20-29
May 19	94.0	27.7	2.9	8.3	—	4	
May 24	45.5	11.8	0.9	6.0	—	1	
May 26	91.3	26.5	5.2	16.3	29.3	1	
May 27	68.5	22.4	6.0	22.0	34.8	1	
May 28	86.5	—	5.3	—	—	0	
May 30	80.0	—	5.0	—	—	1	

Table 3 Quantitative urinary determinations, and medication in Case 6, pancreatic steatorrhea.

Note. Lack of effect of pancreatic extract, and the good result (reduction of number of stools) with raw pancreas, the raw pancreas brought about a better absorption of fats as shown by the rise of ammonia and acid substances in the urine.

The relief from pancreatic stools can be accomplished only by the administration of raw pancreas. The use of any of the commercial extracts has proved to be valueless (see the effect of "Pankreon," table 3). Case 5 has been taking raw pancreas with satisfactory control of his bowels for eight years, every time he omits the pancreas, the steatorrhea returns. Bargen, Bollman and Kepler recently reported the successful control of pancreatic stools by an extract of pancreatic juice administered in capsules, this should prove to be a great boon because raw pancreas has an exceedingly disagreeable, and to many persons, a very revolting taste.

It is interesting to note that the administration of raw pancreas in Case 6 (table 3) improved the absorption of fat a great deal as evidenced by the increase in the acidosis, today with the availability of insulin this ceases to become a clinical threat, but it is worth bearing in mind that uncontrolled steatorrhea may be a factor in producing malnutrition through non-absorp-

* Case 6 is abstracted from a previous publication (Mosenthal, 1912).

tion of fat, table 3 shows that the absorption of glucose or protein was little, if at all, affected by the administration of raw pancreas

SUMMARY

Clinical and pathological studies of diabetes point to the pancreas as the crucial organ responsible for the disturbed carbohydrate metabolism that constitutes diabetes. Chronic pancreatitis resulting from senescent processes is responsible for the very slowly progressive essential diabetes of Naunyn. Acute pancreatitis in its milder form, which is much more common than is generally supposed, probably is the cause for the stormy course, with many acute exacerbations, found in younger diabetics, pancreatitis will result in three sets of symptoms which may develop independently or be combined with one another, these are (1) interference with the carbohydrate metabolism bringing about hyperglycemia, glycosuria, acidosis and coma, (2) disturbance of the fat metabolism manifesting itself in a rise of the blood cholesterol, lipemia, xanthoma, fatty liver and fatty spleen, (3) occlusion of the pancreatic ducts and consequent lack of external secretion of the pancreas into the intestine, causing the characteristic stools and preventing the absorption of fat

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THE VARIABILITY OF BASAL METABOLISM. SOME OBSERVATIONS CONCERNING ITS APPLI- CATION IN CONDITIONS OF HEALTH AND DISEASE¹

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MEANS, discussing the value of the basal metabolic rate, says "It should be remembered that basal metabolic rates are never too low (except when a technical error or an inward leak in the apparatus occurs or when the subject goes to sleep) All the factors which tend to make a reading inaccurate tend to make it too high food, failure to eat properly, emotion, fever and so forth Therefore a single low reading has more significance than a single high one" Similar statements can be found in the writings of nearly all students of metabolism, including Benedict, DuBois, Krogh, Boothby and others

That an important truth of immediate practical interest for the standardization and clinical interpretation of determinations of metabolism is conveyed in such statements is not to be denied, and that adventitious departures from the usual "basal" conditions more frequently raise than lower the measured metabolism is true The term "basal metabolism" for that metabolism measured under defined conditions for standard and clinical purposes usefully emphasized this fact, especially in the early phases of the development of the subject But as Krogh has stated, it might have been better to have used the term "standard metabolism," for the entire concept has been confused by the implications of the term "basal" and the ideas it embodies From the truth that basal metabolism is generally lower than metabolism measured under "non-basal" conditions has grown the fallacious idea that basal metabolism is the *lowest* metabolism From the truth that basal metabolism is less variable than metabolism measured under uncontrolled conditions has insidiously grown an attitude toward basal metabolism as a quantity that is *fixed* These erroneous ideas are never given explicit statement, but they are tacit implications in a considerable amount of work, even important work by the best authorities

We wish in this essay to emphasize that "basal metabolism," as an actual observation is one made under certain defined standard conditions, conditions which while well considered and soundly established, are nevertheless to a considerable degree arbitrary, even if these conditions are rigidly adhered to, the measurement will be *variable*, even as is any biologic observation It

* Submitted for publication August 28, 1937

follows at once that there is no one *lowest* metabolism that has a prerogative to be considered *the* basal metabolism over any other measurement of metabolism made under standard conditions. Were this always realized explicitly, to mention only one consequence there would not be in serious investigations a casual identification of measurements of basal metabolism which are "the lowest observation," "the mean," "the first observation," and so forth for if basal metabolism is a variable, these are not equivalent. It is not to the point at the moment to question whether the distinction between these various representations of basal metabolism is of importance, the fact is that for purposes of certain investigations they are negligible and for others they are essential, but they cannot be *assumed* to be the same.

Once the aspect of variability of metabolism is clearly grasped and deliberately accepted, problems will present themselves, the solution of which will be immediately enlightening, and other old problems will be seen in a different view. It is for these reasons that we have embarked on a careful analysis of a large body of our data, both normal and pathologic, with due regard for the variable characteristics of the material as well as for its central character. Some of these results can be given here.

For the statistical analysis of variability we will make use of the Gaussian curve, the "curve of chance," and the measure of variability appropriate to it as expressed in the "standard deviation." While the correct technical use of statistical methods requires an intensive knowledge of the subject, only a few simple facts need to be known for an investigator unacquainted with the complexities of the subject to understand the significance of those results of our studies which we wish to present here. Therefore, before proceeding to the presentation of some of our findings, we shall review briefly some statistical essentials which will guide what follows.

The Gaussian or "normal" curve is a symmetrical curve, "cocked hat" in shape, and is completely defined mathematically for any given group by two constants, namely, the "mean" and the "standard deviation." The *mean* locates the center of the curve and is the usual *average*. It is calculated as usual by adding all the observations and by dividing the sum by the number of observations. The *standard deviation* (σ , sigma) measures the "spread" or variability of the curve, and it is the value obtained by squaring the difference of each observation from the mean, adding these squares, dividing the sum by the number of observations less one, and finally taking the square root of the result. In other words, $\sigma = \sqrt{\frac{\Sigma \Delta^2}{N-1}}$, where σ is the usual expression for the standard deviation, $\Sigma \Delta^2$ is the sum of the squares of the differences of the individual observations from their mean and N is the number of observations.

The application of the Gaussian curve of chance to problems dealing with biologic data such as we are concerned with arises from the fact that this curve has been found to describe the distribution of biologic observa-

tions, as well as the fluctuations of chance, in a wide variety of situations. It is therefore often referred to as the "normal" curve of distribution. Not all biologic data, of course, can be represented by the Gaussian curve, but if they cannot, that fact is also of significance. If the distribution of the data which are being studied follows the Gaussian curve, then the standard deviation will not only accurately measure the variability of those data in an easily expressed value, but it can also be used directly to give the proportion of cases falling within or outside of any stated limits.

The simplicity of the use of this function is shown in figure 1, where the upper curve represents in the unshaded portion the area within $\pm 0.6745\sigma$ or 1 probable error of the mean, and contains 50 per cent of the observations, and each shaded area in the outer horns of the curve represents 25 per cent of the observations. The middle curve represents in the unshaded portion the area within $\pm 1\sigma$ of the mean, and contains 69.3 per cent of the observations (it can be remembered as roughly $\frac{2}{3}$ of the observations), and each shaded portion outside represents approximately 15 per cent of the observations. The lower curve is the most important because, here, the unshaded center represents the area within $\pm 2\sigma$ of the mean, which is the commonly accepted critical limit. It contains slightly more than 95 per cent of the observations, and each outer horn contains only approximately 2.5 per cent of the observations. It is for the reason that the area within $\pm 2\sigma$ of the mean contains almost all (95 per cent) of the observations that 2σ is usually the limit of "significance." That is, if a value is found to be more than 2σ away from the center of a defined group, it is considered as probably not belonging to that group ("significantly different"), and this probability increases rapidly as the limit of 2σ is exceeded, as can be seen from the shape of the curve.

Bearing this in mind, one can see why the standard deviation should be calculated and the observations compared to the normal curve where possible. Instead of being indefinite about the number of cases that lie beyond any given distance from the mean, we can always refer to the value of $\pm 2\sigma$ and this will represent 95 per cent of the total.

A study of the variability of basal metabolism in normal subjects has just been completed by two of us (Berkson and Boothby), and some of the results may be summarized here. First, the variability of repeated determinations for the same person is to be considered, the intraindividual variability. For successive determinations within the same day the average sigma is 1 calorie per square meter per hour (3.0 per cent of the mean), for successive observations made on successive days, under the usual basal postabsorptive conditions, the average sigma for men and women is 1.5 calories per square meter per hour (4.1 per cent of the mean), and the distribution is Gaussian. The intraindividual variability is somewhat greater for women (1.61 cal per sq meter per hour, 4.7 per cent) than men (1.33 cal per sq meter per hr, 3.5 per cent), and this is attributable prob-

ably to the disturbing effect of the menstrual cycle on the metabolism It is not to be understood that the intraindividual variability is the same for all ages or for different persons of the same age In reviewing the published

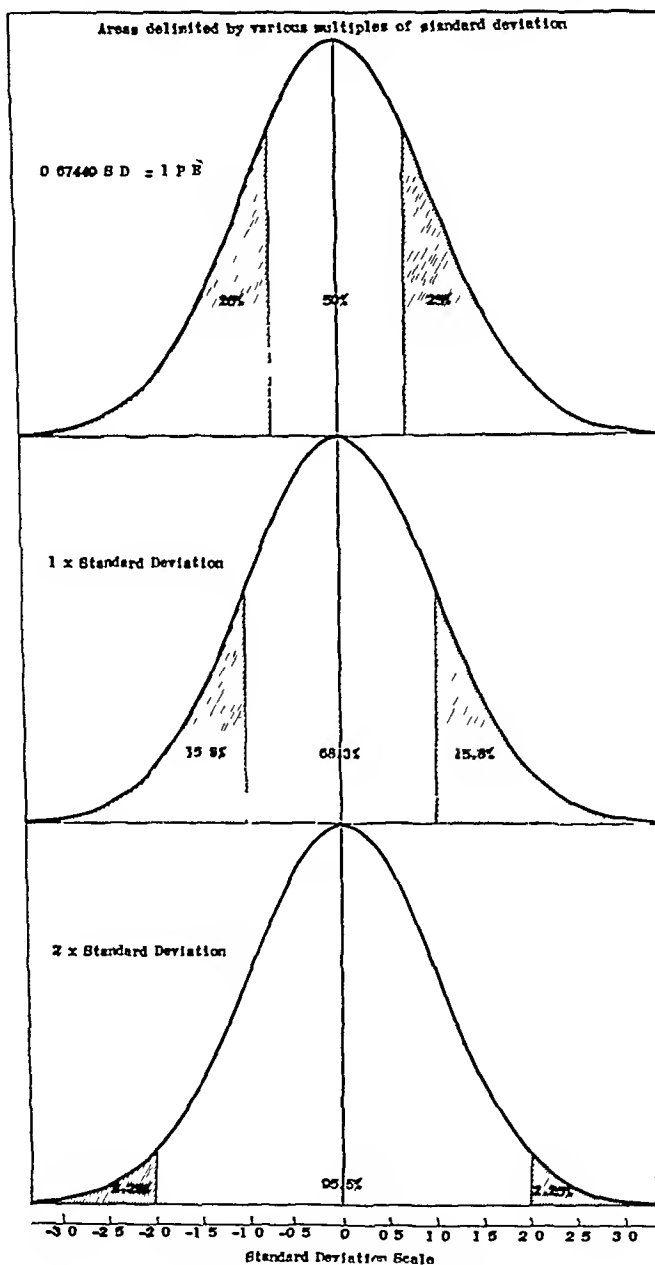


FIG 1 Normal or Gaussian curve

data for the study referred to, we found that Prof F G Benedict had the record for maintaining constancy of metabolism over a long period, the value of his standard deviation being 0.7 calories per square meter per hour (2.2 per cent of the mean)

The variability as between different individuals of the same age, sex, weight, and stature—the interindividual variability—is greater than the intraindividual variability, for it consists of the variation that obtains for the single individual plus that which represents the differences between one individual and another. The sum of these is what we measure in calculating the variability of numerous observations of basal metabolism, each for a different individual (but all of the same sex, age, stature and weight). We found as the interindividual standard deviation for males under 20 years of age, 3.14 calories per square meter per hour (6.5 per cent of mean), and for those 20 years and over, 2.58 (6.7 per cent of mean). For females the standard deviation in the group under 20 years of age was 2.98 calories per square meter per hour (6.8 per cent of mean), and for those 20 years and over, 2.42 (6.9 per cent of mean). These estimates of interindividual variability calculated from single observations made on different individuals is composed, as we have said, of two parts, and we therefore refer to it as the *total* interindividual variability. One part is the variability inherent in repeated determinations for the same person, the intraindividual variability. The other part represents the variability from one person to another, the variability of the “characteristic” or the mean metabolism of different persons.

How much individuals differ from one another apart from their own inherent variability is of considerable biologic interest. However, it is manifestly impracticable to collect a large number of individuals of the same sex, age, stature and weight, and to make for each one a large number of observations to obtain the mean metabolism in order then to calculate directly the variability of those means. Fortunately the value can be estimated indirectly from the calculations already made. Since the total interindividual variability is the sum of the intraindividual variabilities and the variability of means which we are seeking, the variability of mean metabolism can be obtained by subtracting the intraindividual variability from the total. The subtraction is not to be performed by using the standard deviations themselves but rather their squares, because two independent variabilities add their effects as the square-root of the sum of the squares. The square-root of the difference of the squares of the total interindividual variability and the intraindividual variability then, gives the interindividual variability of means. Thus calculated we found for men the value 2.2 calories per square meter per hour (5.8 per cent of the mean), for women 1.81 calories per square meter per hour (5.2 per cent of the mean). Here we found in calories per square meter the variability of men greater than for women, whereas when we considered merely the variability of numerous individual observations we found the female variability larger. We have here, then, the conclusion that if the characteristic (mean) metabolism of the individuals of the species is considered, adult males are more variable than females. Repeated determinations for individual females are, how-

ever, more variable than for males, perhaps as a result of the disturbing influence of the cyclic ovarian function. Therefore, when single determinations for many individuals are used to measure the variability, the total gives a larger net variability for females. It is as though we tried to compare the variability of stature in males and females under circumstances in which the measurement of height in the female was relatively unstable because of posture.

We may now turn to some consideration of observations other than those for normal persons. During the last two decades determinations of the basal metabolic rate as a clinical test have been made in many laboratories and upon thousands of individuals, and it is well established that it is a valuable test for disturbances of the thyroid gland because of its marked increase in hyperthyroid disease and its very low level in hypothyroidism or myxedema. It has at the same time become gradually recognized that the basal metabolic rate is of comparatively little value in the diagnosis of other conditions, in spite of the fact that, in a few, the basal metabolic rate may be definitely affected. The diseases other than those directly associated with the thyroid gland which are known to affect the basal metabolic rate directly or indirectly are the leukemias, the anemias, disorders of the pituitary and of the suprarenal glands, and a few other rare conditions. In addition, on account of respiratory distress, many cardiac patients may have elevated basal metabolic rates, on the other hand, extreme inanition lowers the basal metabolic rate.

During the 10-year period between 1917 and 1926 a large number of patients without thyroid disease were sent to the metabolism laboratory of The Mayo Clinic for the determination of their metabolism. For most of these patients the final clinical diagnosis was some condition which, from everything we know, did not characteristically affect the basal metabolic rate. After excluding, on the basis of a careful and detailed clinical examination, those patients having one of the diseases mentioned in the preceding paragraph which are known to affect the basal metabolic rate, we had for statistical study 7,117 females and 2,397 males, which group for brevity we have designated as the "non-metabolic disease group." In figure 2 is shown the distribution of the observations of the females in this group, and it is seen that the mean of this group is higher, but only by a small amount, 0.7 calories per square meter per hour (1.9 per cent of the standard mean), than a comparable group of normal individuals as judged by comparing them with The Mayo Foundation normal standard. The standard deviation of the distribution is somewhat larger than for a similar normal group, being 3.5 calories per square meter per hour (or 9.7 per cent of the standard mean) instead of 2.5 calories per square meter per hour (or 7 per cent of the standard mean) found for The Mayo Foundation standard. The distribution of the observations for these patients is seen to correspond to the Gaussian curve, as does that for strictly normal individuals. Observations

for the group of males are so similar that it is unnecessary to take space to reproduce the data graphically, the mean for the males is 0.6 calories per square meter per hour above a similar standard normal group (1.7 per cent of the standard mean), and the standard deviation is 3.8 calories per square meter per hour (10.4 per cent of the standard mean)

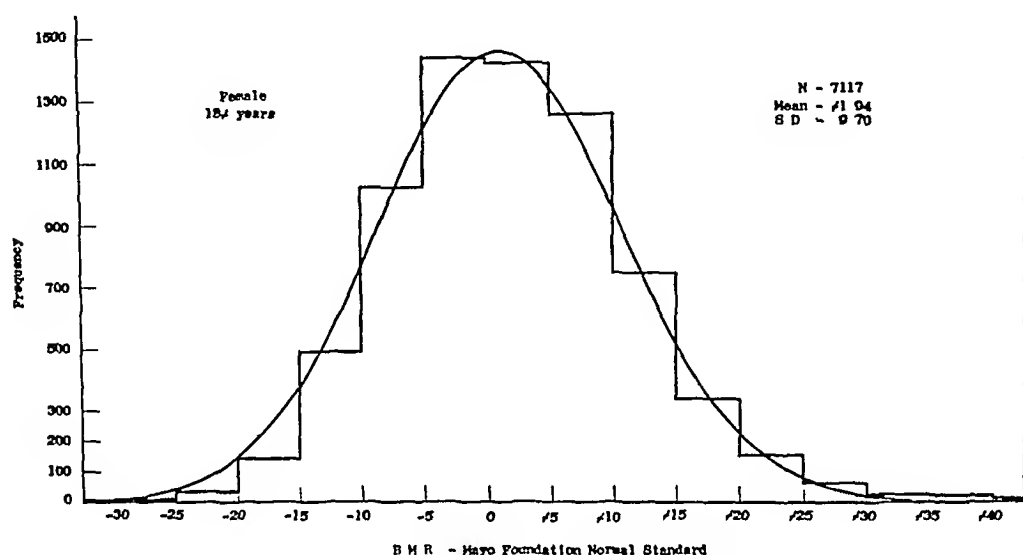


FIG 2 Distribution of basal metabolism for a group of non-metabolic diseases during a period of 10 years

The conclusion drawn from this phase of the study is that the largest group of sick individuals sent for a metabolism test, over half of them suffering from so-called chronic nervous exhaustion or neurasthenia, have a basal metabolic rate on the average very slightly higher (2 per cent), and that they have a greater variability (10 per cent), than strictly normal individuals (7 per cent). Using these round figures and remembering that for distributions following the Gaussian curve 95 per cent of the observations fall within ± 2 sigmas of the mean, we conclude that for such a group of patients, 95 per cent of the observations fall within -18 per cent and $+22$ per cent (2 per cent $\pm 2 \times 10$ per cent) on the usual B M R scale measured from The Mayo Foundation Standard.

Let us now give some attention to the pathologic conditions which we usually associate with disturbances of metabolism—typical disease of the thyroid gland. We consider them in three groups: (1) exophthalmic goiter, (2) adenomatous goiter, with and without clinical hyperthyroidism, and (3) spontaneous myxedema. Figure 3 gives the percentage frequency distribution for these disease groups on a single scale for comparison. The observations are shown in histogram form for the three diseases, comparison is made with a distribution for normal subjects which is represented by a smooth curve obtained from the data on which was based The Mayo Founda-

tion standard In contradistinction to the situation for the normal and non-metabolic disease group, the distributions of the basal metabolism in these thyroid disease groups are not symmetrical Gaussian curves but are

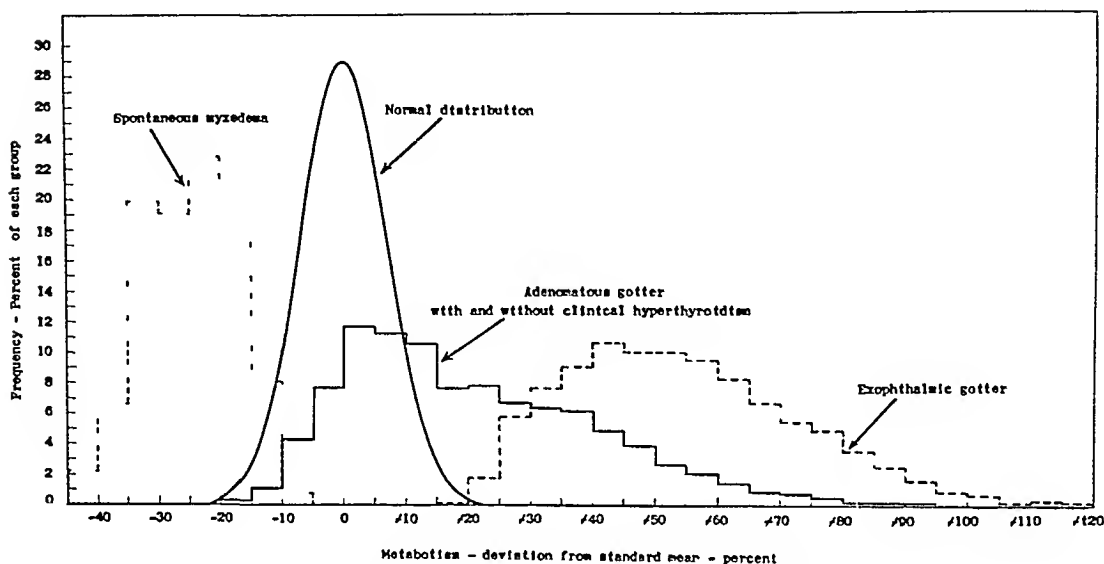


FIG 3 Basal metabolism in three thyroid diseases compared with group of normal individuals
Percentage frequency distribution for each group

“skew” (asymmetrical), the hyperthyroid group being skew in the positive and the hypothyroid in the negative direction. That this skewness will have to be taken into consideration to determine the diagnostic significance to be attached to any given B M R determination which departs from the normal standard enough to be considered as possibly pathologic is manifest.

For the exact calculation of the relative probability indicated by such a finding we will have to have a precise delineation of the frequency curves for the abnormals as well as the normals, a task we have not yet completed. Moreover, for the calculation of the probability which a particular metabolism determination denotes, to be used as a criterion for decision in differential diagnosis, other elements enter besides the relative frequencies of the basal metabolism. First among these perhaps are the relative frequencies of the diseases themselves. During the 1917–1926 period referred to, in which there were seen 7,117 females constituting the non-metabolic disease group, there were 3,385 females with exophthalmic goiter, 3,693 with adenomatous goiter, and only 136 with myxedema. The relative probability of any specific disease indicated by a given finding of metabolism will be in proportion to the actual numbers with this metabolism in this disease. In figure 4 is shown the distribution of the actual frequencies for the various disease groups and for different values of metabolism as they were encountered in the metabolism laboratory during this period. The total areas under each curve represent the total actual frequency of the individuals in

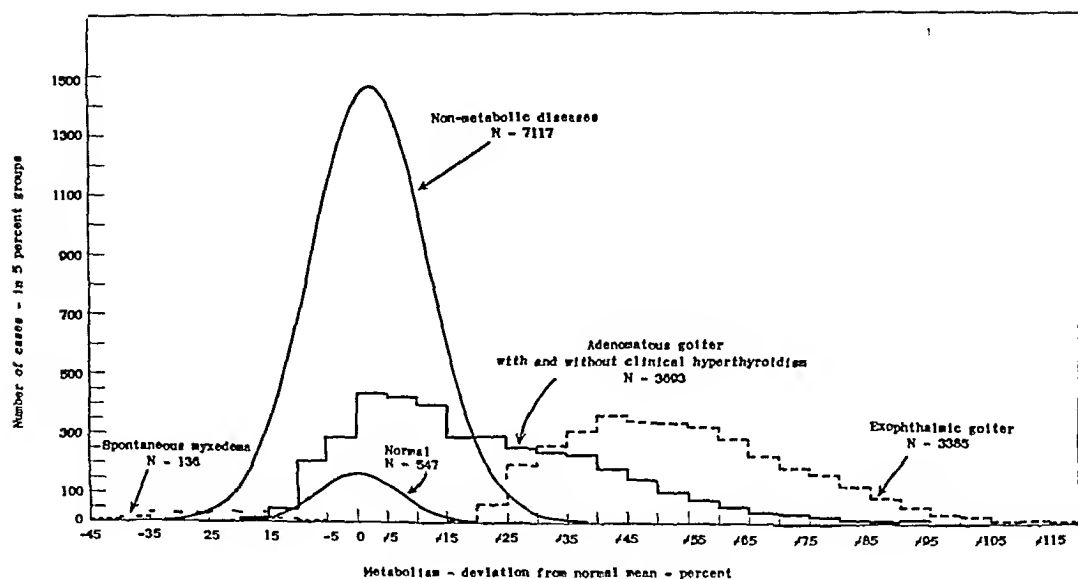


FIG 4 Comparison of normal distribution of basal metabolism with that for three groups of thyroid disease and a non-metabolic disease group. The frequencies are the number of cases corresponding to each group seen during a 10 year period. The total area under each curve is therefore proportional to the number of individuals in the corresponding group sent to the metabolism laboratory during this period.

the corresponding disease group, and the areas under the portion of the curves corresponding to any values of the metabolism give the relative frequencies and therefore probabilities of the diseases indicated by those values of metabolism.

This brief outline is not intended to be a complete analysis of the various questions touched on, but rather to present some ideas which a consideration of the variability of metabolism suggests. While even the precise study of the variability of metabolism of normal and different disease groups and its correlative probabilities will not in themselves make possible a precise differential diagnosis among metabolic and non-metabolic disease—indeed it will only corroborate the impression that clinical observation must play a large rôle here—such studies are not without importance for the diagnostic problems of the clinician.

It may be noted, though we do not wish to elaborate on the point at this time, that the entire curve for adenomatous goiter (with and without clinical hyperthyroidism) is well to the right of both that for the normal individuals and for the group with “non-metabolic diseases.”

In conclusion we wish to emphasize that it is important to study the distribution of cases in each disease group on the percentage basis (that is, on the assumption that one is as likely to encounter a patient with one disease as the other) in order to compare the characteristic basal metabolic findings in each disease. In addition it is equally important to take into consideration the relative frequency with which patients having different diseases present

themselves in a given clinic for study and differential diagnosis if one is to evaluate the probability of a given B M R indicating one or the other condition. This latter point is illustrated in figure 4, in which the graph is based on the actual number of cases occurring in each group in a given period and it is obvious that most of the patients sent to the metabolism laboratory of The Mayo Clinic, who have a B M R between -15 and -20 per cent *do not have mild myxedema*, but rather are normal individuals so far as their metabolic rate is concerned, if, however, as in figure 3, the comparison is made on the assumption, which of course is contrary to the fact, that the number of cases of myxedema is equal to those in the other groups, then it appears as though it were nearly an even chance that an individual with a B M R between -15 and -20 per cent might have myxedema. On the other hand, if the proportion of patients in different disease groups is not very dissimilar, essentially similar deductions will be made whether the frequency is plotted on a percentage basis or on the actual number of cases. For example, the graphs in both figure 3 and figure 4 show that there are many patients with adenomatous goiter who have a B M R between $+15$ and $+20$ per cent, while only relatively few patients who have exophthalmic goiter have a B M R between $+15$ and $+20$ per cent.

Finally it must be recognized that "basal metabolism" as an actual observation, under any defined standard condition, is variable, like any biologic observation, and in consequence no one *lowest* metabolism has a prerogative to be considered *the* basal metabolism over any other measurement made under the defined conditions.

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CARDIAC HYPERTROPHY. ITS RELATION TO CORONARY ARTERIOSCLEROSIS AND CONGESTIVE HEART FAILURE*

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THE cause of hypertrophy of the heart has aroused the interest of pathologists and clinicians for more than three centuries. The hypertrophy of skeletal muscle after increased effort led to the belief that, similarly, cardiac muscle hypertrophied because of increased work. Hypertrophy of the left ventricle in patients with hypertension or aortic insufficiency, and hypertrophy of the right ventricle in pulmonary stenosis or tricuspid valvular disease lent plausibility to this theory.

Certain phenomena, however, associated with hypertrophy of the cardiac musculature have not been readily explicable on the basis of the above hypothesis of increased cardiac work. In animals in which experimental valvular lesions were produced such as aortic insufficiency, increased work of the heart undoubtedly led to hypertrophy, but the degree of hypertrophy occurring even in the most successful experimental instances was much less than that observed clinically in similar lesions¹¹. That cardiac hypertrophy is not due solely to increased work is also suggested by the lack of relationship between the degree of valvular obstruction and the degree of hypertrophy seen in man. These considerations have led observers in the past to consider the possible influence of other factors in the production of hypertrophy.

It appeared from analysis of the literature that the significance of nutritional effects had not been fully established. It seemed to us that more information bearing on this phase of the problem might be obtained by ascertaining in a consecutive series of patients whether those hearts which showed advanced arteriosclerosis differed in weight from those showing little or no such change. No case was included in the series that showed evidences of hypertension, syphilis, rheumatic heart disease, anemia, or other factors which would give rise to increased work on the part of the heart. Patients who had congestive failure associated with advanced coronary sclerosis were considered in a separate group in order to study the importance of congestive failure itself in the production of hypertrophy.

The purpose of this communication is to present the results of this study.

* Received for publication August 31, 1937.

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and to appraise the significance of two factors in the causation of cardiac hypertrophy (1) a diminished coronary circulation, (2) the influence of chronic congestive heart failure

METHODS AND RESULTS

To evaluate the rôle of coronary artery disease in producing hypertrophy of the heart, the cardiac weights of an unselected consecutive series of patients that had come to postmortem examination were studied. To learn the significance of a diminished coronary circulation uncomplicated by other factors, all cases with any antemortem evidence of congestive failure and all cases showing signs or symptoms of conditions acknowledged to be of possible significance in the production of cardiac hypertrophy such as hypertension, valvular heart disease, mediastino-pericarditis, long continued anemia, leukemia, or thyrotoxicosis were eliminated. Hearts showing slight degrees of aortic stenosis of arteriosclerotic origin were also excluded. To rule out the existence at any previous time of arterial hypertension is always difficult since the fluctuations in blood pressure in this condition always render it theoretically possible that the blood pressure may have been elevated prior to the first recorded physical examination or between the various examinations listed. In order to minimize this possible error, the past history was carefully investigated in each case and the blood pressure measurements obtained on previous admissions in other hospitals, by outside physicians and by life insurance examinations were considered. The upper limit of normal blood pressure was taken as 160 mm mercury systolic and 90 mm mercury diastolic. The blood pressure data obtained during a final illness were considered with reservations. Cases in which death was associated with shock due to acute coronary occlusion, intestinal obstruction, perforation of a viscus, or hemorrhage were, of course, excluded unless evidence of a normal blood pressure prior to the final illness was available.

The heart weights of a consecutive group with advanced coronary disease were then compared with a similarly consecutive group showing little or no coronary disease, all cases with the above mentioned factors that might produce cardiac hypertrophy having been eliminated. The only error inherent in this separation of the two groups would be that of possibly overlooking involvement of a portion of some coronary branch, this error would lead to the false inclusion of some cases in the group with little atherosclerosis and so make any differences between the two groups less striking.

In classifying the degree of atherosclerotic involvement of the coronary vessels, the following criteria were employed: grade I, all large branches free from atheromatous changes, grade II, scattered atheromata but no ulcerations or striking changes in the surface of the intima, grade III, the intima covered with atheromatous plaques and inclusion in the pathological report of a definite statement by the examining pathologist to the effect that

there was no narrowing of the lumen at any point, grade IV, as in grade III with one or two sites of slight narrowing, grade V, as in grade IV but with greater degree of narrowing, grade VI, complete obliteration of one major coronary branch such as the left anterior descending, left circumflex or right coronary with little or no narrowing of other branches, and grade VII, complete obliteration of one branch but with marked changes and narrowing in another or all coronary branches

Figure 1 shows the distribution of cardiac weights in 31 consecutive subjects with advanced coronary disease (grades IV–VII) as compared with 38 cases showing little coronary disease (grades I and II). The ages in the group with marked coronary arteriosclerosis varied from 49 to 80 years and averaged 62 years, in the patients with little arteriosclerosis the ages varied from 50 to 76 years and averaged 61 years, nine of the former

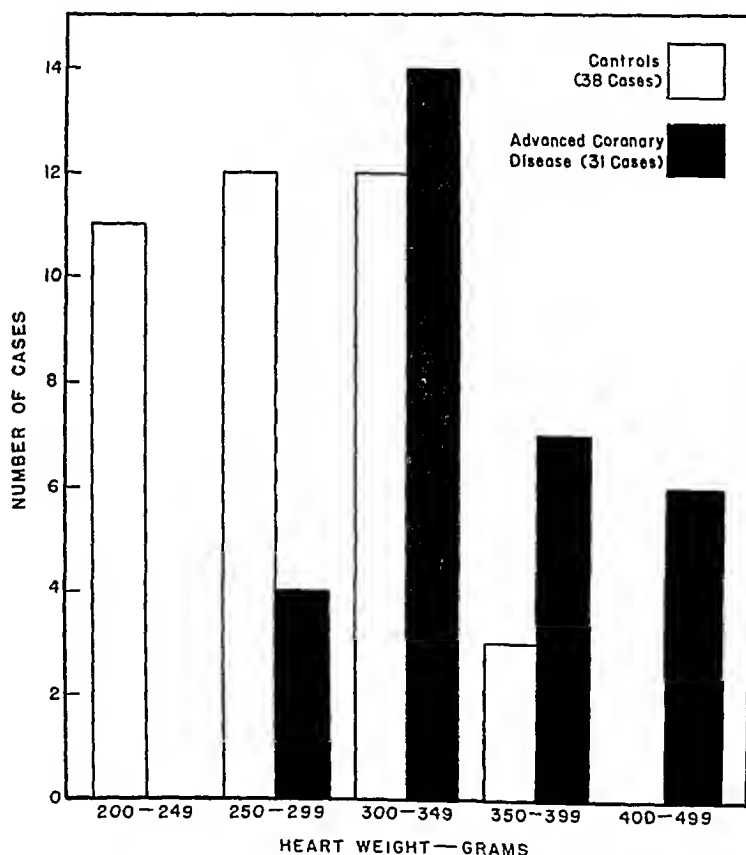


FIG 1 Comparison of heart weights in patients with advanced coronary sclerosis with those showing little or no coronary sclerosis

group and 14 of the latter group were females (Table 1). Of the 31 hearts showing advanced coronary arteriosclerosis, eight were classified as grade VII, six, grade VI, fifteen, grade V, and two, grade IV. Nine of the 31 cases died of coronary thrombosis. Of the 38 hearts showing but little coronary arteriosclerosis, 26 were classified as grade I, 12 as grade II

TABLE I

Data in Series of Patients with Little or No Coronary Arteriosclerotic Heart Disease

No	Age	Sex	Ht Wt Gm	Degree Coronary Disease	Blood Pressure at Final Illness		Cause of Death
					Systolic	Diastolic	
1	65	F	200	1	110	60	Pneumonia
2	76	M	200	2	116	72	Carcinoma of stomach
3	58	M	200	2	142	62	Carcinoma of stomach
4	72	M	210	1	100	55	Pneumonia
5	55	F	210	1	90	60	Hodgkin's disease
6	64	M	215	1	110	64	Carcinoma of colon
7	53	F	220	1	120	85	Carcinoma of colon
8	51	F	220	1	140	90	Pneumonia
9	55	F	220	1	120	65	Pneumonia
10	72	M	240	2	135	90	Carcinoma of lung
11	68	F	240	2	140	60	Pneumonia
12	68	F	250	1	145	85	Carcinoma of cecum
13	63	M	250	2	150	90	Pneumonia
14	63	M	250	1	88	60	Carcinomatosis
15	58	M	260	1	120	70	Carcinoma of colon
16	62	F	260	2	90	54	Septicemia
17	56	F	260	1	128	78	Peritonitis
18	73	F	270	2	110	70	Pneumonia
19	60	M	270	2	128	60	Pneumonia
20	52	M	280	2	150	60	Malignancy of spine
21	73	M	280	1	125	70	Liver abscess
22	55	M	280	1	114	70	Carcinoma of stomach
23	51	F	280	1	90	55	Peritonitis
24	65	M	300	2	110	74	Post-operative shock
25	50	M	300	1	95	65	Carcinoma of esophagus
26	64	M	300	2	122	88	Carcinoma of colon
27	55	M	300	1			Pneumonia
28	51	F	310	1	110	82	Peritonitis
29	57	M	320	1	120	80	Carcinoma of lung
30	59	M	320	1	130	75	Pneumonia
31	62	F	320	2	140	90	Pneumonia
32	65	M	320	1	120	60	Pneumonia
33	76	M	320	1	150	90	Carcinoma of liver
34	51	M	340	1	130	80	Peritonitis
35	60	M	340	1	140	80	Pneumonia
36	62	M	350	1	124	70	Hemorrhage of gastric ulcer
37	59	M	360	1	120	80	Carcinoma of esophagus
38	51	F	380	1	130	90	Pneumonia
			Average Weight	275	M 24	Grade 1 = 26	
			Age	61	F 14	2 = 12	

The range of distribution of cardiac weights of the cases with advanced coronary arteriosclerosis was definitely higher and the average weight was 348 grams. The mean heart weight of the cases with little coronary atherosclerosis was 275 grams. Although the group with marked coronary arteriosclerosis showed a higher weight distribution, there were few very heavy hearts, the heaviest weighed 440 grams and only six weighed more than 400 grams. Blood pressures taken a few months to two years prior to the final illness were obtained in cases 30, 28, and 20 to 26 inclusive. The pressures varied from 110 to 142 mm systolic and from 60 to 80 mm diastolic. The blood pressures in the remaining three cases with heart

weights above 350 gm were obtained soon after admission to the hospital before the terminal stages of the illness, in two of these latter three instances the history recorded that previous examinations showed no evidence of an elevated blood pressure

TABLE II
Data in Series of Patients with Advanced Arteriosclerotic Heart Disease

No	Age	Sex	Ht Wt Gm	Degree of Coronary Disease	Blood Pressure at Final Illness		Cause of Death
					Systolic	Diastolic	
1	63	M	260	5	140	88	Pneumonia
2	69	M	280	5	134	72	Carcinoma
3	59	M	290	5	110	60	Carcinoma of stomach
4	58	M	290	6			Coronary thrombosis
5	77	M	300	6	142	64	Coronary thrombosis
6	73	M	300	5	150	85	Carcinoma of sigmoid
7	63	F	300	6	118	64	Amputation and sepsis
8	52	M	310	7	150	90	Pericolic abscess
9	60	M	314	7	140	70	Pneumonia
10	53	F	320	5	124	80	Menigitis
11	80	F	330	7	160	90	Pneumonia
12	50	M	330	5	150	60	Brain tumor
13	57	M	340	5	140	80	Lymphatic leukemia
14	54	F	340	5	100	40	Coronary thrombosis
15	72	M	340	5	150	70	Carcinoma of colon
16	66	M	340	5	130	80	Central nervous system disease
17	75	F	340	6	130	80	Coronary thrombosis
18	49	F	340	7	80	40	Coronary thrombosis
19	59	M	350	4	132	110	Pneumonia
20	68	M	360	7	140	70	Pneumonia
21	58	M	360	5	120	80	Coronary thrombosis
22	62	M	380	7			Hemorrhage of gastric ulcer
23	54	M	380	6	130	100	Coronary thrombosis
24	62	M	380	5			Coronary thrombosis
25	63	F	380	7	100	75	Coronary thrombosis
26	73	F	400	6			Pneumonia
27	72	M	410	4	140	75	Carcinoma of stomach
28	49	M	420	7	146	78	Carcinoma of lungs
29	75	M	420	5	135	80	Pneumonia
30	64	F	440	5	135	60	Cirrhosis of liver
31	56	M	440	5	140	85	Brain tumor

To determine the influence of congestive failure in the production of cardiac hypertrophy, a consecutive series of necropsy reports of patients in whom congestive heart failure had occurred before death were examined. Cases in which hypertension, valvular disease, mediastino-pericarditis, or any of the other accepted causes of cardiac hypertrophy had been present were excluded. A series of 17 cases remained for study, 15 of which showed advanced coronary arteriosclerosis, falling in groups V to VII above (table 3). The cardiac weights of this series were compared with the previously mentioned series of cases showing advanced coronary atherosclerosis but no congestive failure (figure 2). The higher incidence of

greater heart weights in cases with congestive failure is striking (figure 2) With but one exception, the cases with congestive failure showed cardiac weights of 400 grams or over, 11 being 500 grams or over Of the latter 11, five were 600 grams or over These findings are in contrast with those in the group with advanced coronary atherosclerosis but no congestive failure

TABLE III
Congestive Failure

No	Sex	Age	Ht Wt Gm	Degree of Coronary Disease	Duration of Congestive Failure
1	F	70	330	6	Few weeks
2	M	60	400	7	Few weeks
3	M	75	400	7	Few months
4	M	65	450	6	2½ years
5	M	65	450	5	2½ years
6	M	55	490	7	One month
7	M	59	500	5	1-6 years?
8	M	63	500	7	1½ years
9	M	63	520	5	One year
10	M	58	520	5	2 years
11	M	67	540	7	4 years
12	M	68	580	7	2 years
13	M	58	600	2	2 years
14	M	64	720	7	3-4 months
15	M	59	730	7	13 years
16	M	57	735	7	4 years
17	M	77	740	3	1½ years

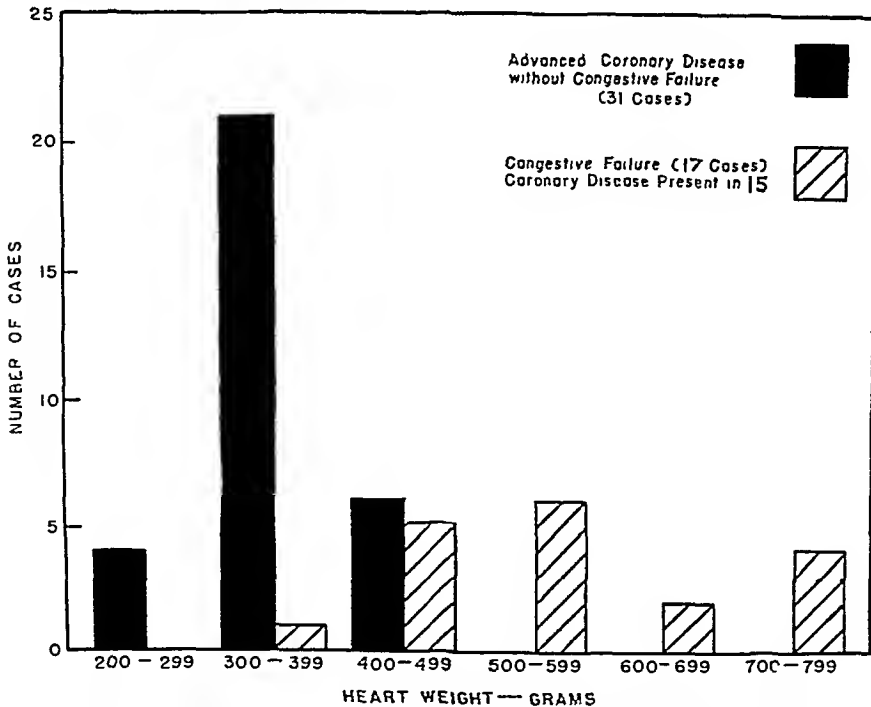


FIG 2 Cardiac weights in patients with advanced coronary disease compared with heart weights in patients with congestive failure

in which no cardiac weight above 440 grams was observed. In addition to the data presented above, the progressive increase in heart size could be followed by frequent roentgenograms in two patients with recurrent attacks of congestive failure due to coronary atherosclerosis who eventually came to postmortem examination.

CASE REPORTS

Case 1 (L. S.) This male, aged 63, had had angina pectoris for seven and a half years, and during the past year was admitted to the hospital three times for congestive failure. On his first admission on December 10, 1935, he complained of palpitation, dyspnea on exertion, cough and nocturnal dyspnea of two months' duration. Physical examination showed cardiac enlargement, gallop rhythm, râles at both bases, an enlarged tender liver, and edema of the legs and over the sacrum. A seven foot roentgenogram taken in the out-patient clinic on June 4, 1929, showed a transverse cardiac diameter of 14.7 cm (table 4). A second roentgenogram taken on November

TABLE IV
Cardiac Enlargement in the Course of Congestive Heart Failure

L. S.	6/4/29	11/13/34	11/27/35	2/2/37
	cm	cm	cm	cm
R	5.9	4.6	7.2	7.1
L	8.8	9.1	11.3	12.5
T	14.7	13.7	18.5	19.6
Ch	29.5	30.0	28.2	29.6
G. V.	7.0	6.8	8.0	7.9
L	13.9	15.5	17.5	
B	10.5	11.3	11.7	
H. B.	3/17/30	11/2/32	3/13/33	3/23/33
	cm	cm	cm	cm
R	6.2	9.5	9.4	10.2
L	12.1	12.6	12.4	12.6
T	18.3	22.1	21.8	22.8
Ch	28.5	29.4	28.0	30.2
G. V.	7.5	11.2	8.0	8.4
L	17.5	20.0	21.1	21.0
B	13.8	17.1	15.8	17.8

13, 1934, showed a transverse diameter of 13.7 cm. Thus, there had been no change in the cardiac measurements during a period of five years. Just prior to this admission to the hospital, however, the roentgenogram showed a transverse cardiac diameter of 18.5 cm, an appreciable increase presumably in part due to acute dilatation accompanying the congestive failure. Seven days after this admission he was discharged improved, but a few months later, March 30, 1936, he was readmitted for congestive failure and remained in the hospital for 14 days. Eight months later, January 14, 1937, he was admitted a third time for congestive failure. At the end of the first week he was free of edema and allowed to be up and about the wards. A seven foot roentgenogram was then taken on February 2, 1937, and this showed a transverse diameter of 19.6 cm. The increase in cardiac size during the past year was greater than apparent from the roentgenographic measurements, for the increased transverse diameter of 18.5 cm the year before was associated with congestive failure presumably associated with some acute dilatation. He died suddenly on February 3, 1937, and postmortem examination revealed no cardiac dilatation. The heart weighed

500 grams The coronary distribution was studied with injection and roentgenographic methods by Dr Monroe Schlesinger and found to be the seat of extensive coronary sclerosis and occlusion A tremendous collateral circulation had developed The changes in heart size are recorded in table 3 and figure 3 The cardiac size showed a progressive increase during the period of congestive failure

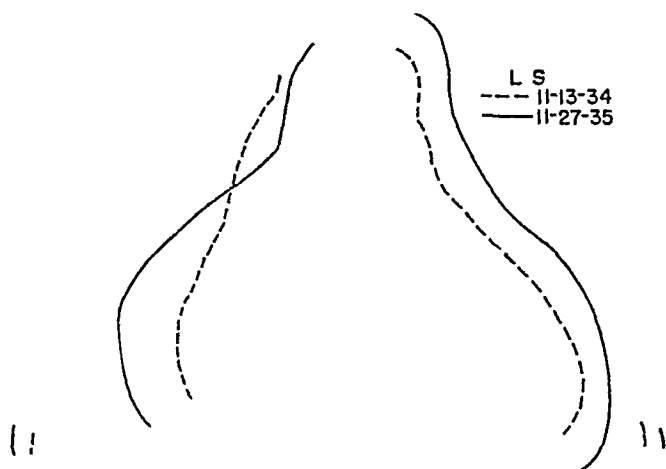


FIG 3 Case 1 Increase in heart size in course of congestive heart failure

Case 2 (H B) This male, aged 57, was admitted to the hospital on March 8, 1930, complaining of dyspnea on slight exertion and edema of the ankles of two weeks' duration Examination showed cardiac enlargement and auricular fibrillation, and the electrocardiogram showed bundle branch block In the course of the next three years with the exception of a few months he was not free from congestive failure and was almost completely confined to bed Transverse diameters of subsequent seven foot roentgenograms showed a progressive increase in heart size (table 3) Necropsy on January 26, 1934, showed evidence of an old mitral lesion with calcification of the mitral ring, thickening and some retraction of the valve cusps There was, however, no appreciable incompetency of the valves The slight mitral lesion had undoubtedly been present for many years, and therefore it probably did not have any influence on the cardiac enlargement during his recent illness The coronary arteries showed an extreme degree of sclerosis with numerous points of occlusion The heart weight was 735 grams Figure 4 shows the increase in size in the course of heart failure

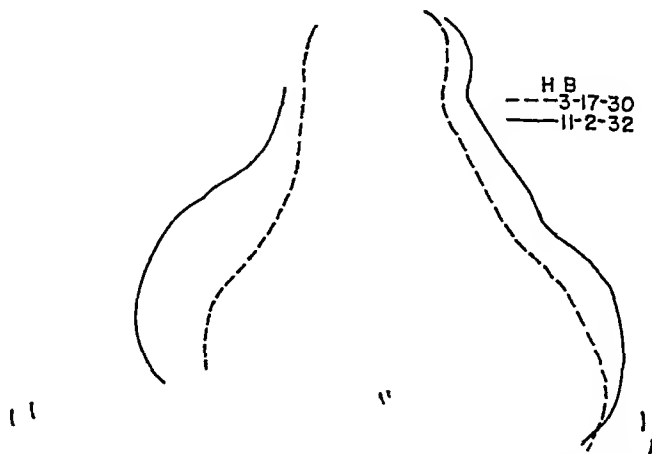


FIG 4 Case 2 Increase in heart size in course of congestive heart failure.

DISCUSSION

The foregoing results do not solve the problem of cardiac hypertrophy but are of value in appraising the etiological importance of two contributory influences, coronary arteriosclerosis and congestive failure, which are frequently operative but often neglected in discussions on the subject. The early studies of Corvisart in 1806,³⁵ and the emphatic views of Cohnheim³⁶ in 1882, as well as the supporting opinions of many later investigators, have stressed increased work as the stimulus causing hypertrophy of the cardiac musculature. Clinical experience, as well as many experimental investigations, has thrown doubt, however, upon the validity of the view that cardiac hypertrophy can always be ascribed entirely to increased work. Practically all investigators agree that cardiac hypertrophy is found under conditions demanding increased work of the heart but many observers have stated that various other factors may play a contributory or even a dominant rôle, their views may be conveniently grouped under the following headings:

1 *Elevated Metabolism* In thyrotoxicosis the heart weight has been found increased by numerous observers. This increase may be due (1) to coincident marked cardiovascular disease or latent heart disease made manifest by the hyperthyroidism, (2) to overwork consequent to the elevated metabolic rate, or (3) to a specific toxic effect on the heart. Only in the latter two instances can the hypertrophy be ascribed to the thyroid disease itself. Failure to evaluate coincident organic disease has vitiated many of the reports on this subject and has led to varied opinions^{13, 27}. An analysis of the available data indicates that cardiac hypertrophy occurs only infrequently in uncomplicated thyrotoxicosis and then only to a slight degree^{21, 22}. Experimentally, cardiac hypertrophy has been produced by the administration of thyroid, but the conditions of the experiments and the criteria of hypertrophy employed do not permit unquestionable clinical application of the results^{23, 24, 25, 26}. In chronic lymphatic leukemia in which there is an elevated metabolic rate unassociated with hyperthyroidism, post mortem examination has revealed the average heart weight increased 75 grams above the normal¹⁶. It is of interest that in frizzle fowl in which species the metabolism is elevated, the hearts are reported as definitely hypertrophied^{3, 4}.

2 *Increased Physical Exertion* There is a divergence of opinion regarding the effect of exercise on the weight of the heart, some maintaining that the heart weights of athletes fall within the range of normal for individuals of the same size and age who have not engaged in prolonged strenuous exercise, while others believe that prolonged exercise leads to definite hypertrophy. In accord with this latter view Tung and his co-workers²⁰ state that definite cardiac enlargement of the heart as seen by roentgen-ray was found in 45 per cent of their series of 46 ricksha pullers, no heart weights, however, are given. Steinhaus²⁹ has discussed this aspect of the problem in detail.

3 *Anemia* Cardiac hypertrophy at post mortem has been found in pernicious anemia in the absence of other factors to account for it⁵ Similarly, Porter¹⁷ by roentgenographic studies found an increased heart size in the anemia associated with hookworm disease and obtained suggestive evidence of hypertrophy, inasmuch as the heart size, while becoming smaller after alleviation of the anemia, did not return to normal

4 *Coronary Arteriosclerosis* Miller and Weiss¹⁵ reported 19 cases with advanced arteriosclerotic involvement of the coronary vessels unassociated, however, with any evidence of cardiac hypertrophy, leading them to the conclusion that advanced coronary artery disease does not necessarily cause gross cardiac hypertrophy The cardiac weights in two instances were, however, 350 and 400 grams Similarly, Horine and Weiss¹² found no roentgenological evidence of cardiac enlargement in 20 patients with coronary thrombosis observed by periodic seven foot roentgenograms from five months to nine years after the initial attack It is not likely that small changes in heart weight would be readily translated into changes in the seven foot roentgenogram Bartels and Smith,¹ on the other hand, in a study of patients with myocardial infarction found heart weights of 400 grams or more in 26 of 42 patients, the largest heart weighing 715 grams These authors stated that in none of these 42 cases was there any evidence of any condition commonly supposed to produce hypertrophy No statement is made, however, regarding the presence or absence of congestive failure Nemet and Gross¹⁸ in their study of the inter-relationship of arteriosclerotic heart disease and chronic congestive failure report 11 patients of their series of 100 who showed no evidence of congestive failure Of these 11 cases, seven showed heart weights less than 400 grams, two were above 400 grams and two showed generalized microscopic hypertrophy of muscle fibers Coronary artery disease sufficiently marked to cause coronary thrombosis was found to be the sole factor in producing cardiac enlargement in only 11 of a series of 128 patients with enlarged hearts reported by Parkinson¹⁹

5 *Other Defective Nutritional States* Cardiac hypertrophy has been observed experimentally after the injection of spartein sulphate and adrenaline chloride⁷ In two cases in the literature in which the left coronary artery arose from the pulmonary conus^{2,6} marked left ventricular hypertrophy was found in the absence of valvular defects, the supply by the left coronary artery of venous blood under the decreased pulmonary arterial pressure was evidently the causal factor That cardiac enlargement might be due to defective nutrition of the heart muscle because of deficient coronary blood supply consequent to the fall of mean arterial pressure was advanced as a cause of hypertrophy by Lewis and Drury³¹ in their study of the pathological physiology of arteriovenous aneurysm These authors further stated that defective nutrition is probably the cause or contributing cause of cardiac hypertrophy in such conditions as aortic regurgitation, coronary arteriosclerosis, anemia or any condition in which the output of the heart is

decreased or the mean arterial pressure is much reduced Willius and Smith³² report hypertrophy of the heart in several children who survived for only short periods following their first rheumatic infections and in whom inflammatory lesions of the heart were widespread Willius and Smith conclude that the severe myocarditis of these children was the chief factor contributing to the production of cardiac hypertrophy, since the valvular deformity was relatively slight The coexistence of congestive heart failure in at least three of these four cases makes interpretation of their findings difficult Myocardial degeneration due to unknown causes has been found in cases of marked idiopathic hypertrophy of the heart¹⁴

6 *The "Injury Theory" of Cardiac Hypertrophy* Among the numerous other theories to account for cardiac hypertrophy, that first enunciated by Horvath,²⁸ later supported by the pathological studies of Albrecht³³ and more recently strengthened by the important experimental observations of Eyster^{8, 9, 10} seems most satisfactory, since it provides a common denominator according to which practically all forms of hypertrophy become understandable Horvath²⁸ strenuously objected to the work theory of hypertrophy and asserted that the fundamental cause of hypertrophy of any muscle from whatever stimulus lay in stretching of muscle fibers greater than normal This stretching acts as a common causal factor of both work and of hypertrophy, the latter two being results and in no way interrelated as cause and effect He stated that the uterus hypertrophies without work during pregnancy and that the eye muscles and diaphragm accomplish much work but are not under tension and do not hypertrophy Albrecht³³ described histologic evidences of muscle injury preceding hypertrophy, and stated that interference with the normal nutrition of the heart preceded hypertrophy The experimental observations of Eyster and his associates^{8, 9, 10} are of considerable importance These investigators produced aortic regurgitation in dogs, following which roentgenograms showed definite acute dilatation of the heart, reaching its maximum on the third to sixth day and disappearing by the tenth day Subsequently, hypertrophy gradually developed Similar dilatation and subsequent hypertrophy were induced by creating aortic stenosis by constriction of the ascending aorta with a rubber band In one group of animals the band was removed after from three to six days when dilatation had reached its maximum and before hypertrophy had occurred The hearts subsequently hypertrophied to an extent comparable to that occurring in the dogs in which the bands were allowed to remain intact During the period of initial dilatation the muscle wall was thin and stretched, and hydropic degeneration became evident After hypertrophy had developed there was an increase in size of the individual fibers without increase in fibrous tissue The hypertrophy was therefore considered to be a reaction to injury brought about by the sudden dilatation

The above theory as to the cause of hypertrophy was termed by Eyster⁸

the "theory of injury" and would seem to provide a common denominator for most of the various types of hypertrophy. Thus, any condition which imposes an increased initial tension on cardiac muscle such as hypertension, valvular defects, or congenital defects is in accord with this theory. Hypertrophy in conditions in which prolonged impaired nutrition of the heart muscle exists is likewise readily understandable for the consequent dilatation or stretching again acts as the causal factor. The experimental studies of hypertrophy following inflammation or the injection of toxins, the occurrence of hypertrophy in leukemia and pernicious anemia, the left ventricular hypertrophy in some instances of so-called idiopathic hypertrophy in which the left coronary artery carries venous blood at lower pressures because of its anomalous origin from the pulmonary artery are instances which are in accord with this concept.

Our own observations presented in this communication provide strong clinical support to the "injury theory" of Horvath, Albrecht and Eyster as well as affording insight regarding the degree to which hypertrophy of the heart may be ascribed to coronary arteriosclerosis itself. The fact that the group of patients with moderate or advanced arteriosclerosis were similar in all other respects, such as age, clinical condition, etc., to the group with slight or no coronary arteriosclerosis permits one to conclude that slight or even moderate cardiac hypertrophy is frequently, though not necessarily, associated with the more advanced degrees of arteriosclerotic involvement of the coronary arteries. The occurrence of cardiac hypertrophy in many conditions in which the work of the heart is increased makes it difficult to ascertain the degree to which other factors are operative in the production of the hypertrophy, in the patients described above, conditions requiring increased work by the heart were not present.

It is reasonable to infer on the basis of the involvement of the coronary vessels and the presence of diffuse focal changes noted in such hearts that the nutrition of the musculature is impaired. Dilatation or stretching of the fibers under such circumstances leads to subsequent hypertrophy, when the degree of impairment is greater, more marked consequences ensue and congestive failure supervenes. As shown by Starling and his associates,³⁴ such dilatation is in the nature of a beneficial response since it enables the heart for the moment to increase its capacity for work. The fact that all patients with considerable coronary arteriosclerotic involvement do not show hypertrophy is probably due to the development of adequate collateral circulation which compensates in such cases for the localized diminished blood supply.

Our data also indicate that the existence of congestive failure in itself leads to the development of hypertrophy. It has often been inferred that the largest hearts in congestive failure were enlarged initially and fail because of the previous dilatation and hypertrophy. According to this concept, congestive heart failure is the failure of the hypertrophied heart. If this were so, one would expect to find such large hearts before the onset of

failure in at least a few instances in an unselected group of patients with advanced coronary arteriosclerosis. Slightly increased weights were observed by us in this group (table 1) but the degree of hypertrophy was never great.

In brief, our data indicate that with the lesser degrees of coronary arteriosclerosis the heart undergoes little or no hypertrophy, with more severe involvement a slight degree of hypertrophy is encountered presumably due to impaired nutrition of the muscle fibers causing them to undergo stretching and consequent hypertrophy. In patients who have suffered from congestive failure the weights of the hearts are considerably increased. This finding might be interpreted as being the direct result of more advanced degrees of arteriosclerotic involvement of the heart, the concomitant congestive failure playing no significant rôle. Our data, however, suggest that while the advent of congestive failure may be due to severe impairment of nutrition, the more striking degrees of cardiac hypertrophy observed in such patients are largely consequent to the development of congestive failure itself and rarely occur in its absence. In accord with this concept, the degree of cardiac hypertrophy seemed generally proportional to the severity and duration of congestive failure.

SUMMARY AND CONCLUSIONS

The purpose of this communication is to present the results of the findings in patients with various degrees of coronary arteriosclerosis in order to appraise the significance of two factors in the causation of cardiac hypertrophy: (1) a diminished coronary circulation, (2) the influence of chronic congestive failure.

The cardiac weights of a consecutive series of patients were studied to learn whether those hearts which showed advanced arteriosclerosis differed from those showing little or no such change. No case was included that showed evidences of hypertension, syphilis, rheumatic heart disease, anemia, or other factors which would give rise to increased work on the part of the heart.

The cardiac weights of the cases with advanced arteriosclerosis showed a definitely higher range of distribution than the cases in a comparable series with but little coronary arteriosclerosis. There were, however, few greatly hypertrophied hearts in the cases showing advanced coronary arteriosclerosis, the heaviest weighing 440 grams and only six of the 31 weighing more than 400 grams. In a comparable series of patients in whom congestive failure was also present, 16 out of 17 showed heart weights above 400 grams and eleven above 500 grams.

The data indicate that with the lesser degrees of coronary arteriosclerosis the heart undergoes little or no hypertrophy, with more severe involvement a slight or moderate degree of hypertrophy is encountered presumably due to impaired nutrition of the muscle fibers which causes them to undergo

stretching and consequent hypertrophy. In patients who have suffered from congestive failure, the weights of the hearts are considerably increased.

These results support the "injury theory" of Horvath, Albrecht, and Eyster of the causation of cardiac hypertrophy rather than the widely held "work hypertrophy theory."

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EFFECT OF VITAMIN C ON THE CULTURE OF H_{37} TUBERCLE BACILLUS*

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MANY infectious diseases have been shown to be accompanied by a subnormal urinary excretion of cevitamic acid—vitamin C. Presumably the cevitamic acid has been altered or destroyed, directly or indirectly, by the action of the infecting organisms. That this may be true is shown by the development of scurvy in spite of ample gastrointestinal intake of cevitamic acid in the food. Marin¹ reports such an instance and thinks the destruction of the vitamin was due to *Bacillus coli* or paratyphoid B in the intestine. His patient failed to recover by oral anti-scorbutic treatment. Steppe² showed this destruction of vitamin C experimentally. He found that various types of coli and paratyphoid react differently on vitamin C under the same cultural conditions. The pH apparently had no influence. Some of the organisms destroyed the vitamin in 24 hours. On the other hand, the vitamin has a definite influence on some bacteria and upon bacterial and other toxins. It will not, however, replace the growth promoting substances found in some media (Koser et al.³). Von Gagyi⁴ studied the effect of various organisms upon vitamin C and the effect of vitamin C upon the same organisms. He worked with coli communis, paracoli, typhoid, paratyphoid, dysentery, saprophytes and the tubercle bacillus. He found that the tubercle bacillus lived at least 70 hours upon media containing five parts cevitamic acid per 1,000. A change in virulence of these tubercle bacilli was not determined up to the time of his publication. Boissevain and Spillane⁵ found that growth of H_{37} tubercle bacilli occurred only after the cevitamic acid content had fallen below 0.001 per cent. The synthetic cevitamic acid content of the medium was kept more or less constant by the addition of cevitamic acid every three days. Although when this was done the pH was within the range of growth, no growth took place when the concentration of the vitamin was 0.001 per cent or higher. However, no protective action against H_{37} was produced in guinea pigs by the administration of 50 times the antiscorbutic dose of cevitamic acid. This confirmed the work of others who failed to find such a protective action.

In a series of experiments with cevitamic acid given by vein, Heise, Martin and Schwartz⁶ found that the sensitivity to tuberculin was lessened and the blood sedimentation speed reduced in a proportion of tuberculous patients, although Heise and Martin⁷ could demonstrate no protective action.

* Received for publication July 24, 1937.

From the Trudeau Clinical and Research Laboratory, Trudeau, N. Y.

of cevitic acid against tuberculous infection in guinea pigs, in a preliminary test. Interest was naturally aroused as to the possible effect of cevitic acid upon the growth of the tubercle bacillus upon a medium of known content.

EXPERIMENTAL PROCEDURE

Twenty cc of Proskauer and Beck's synthetic medium were placed in each of four flasks. To two of them 100 mg of cevitic acid were added. The H₃₇Rv (Steenken) variant of tubercle bacilli was seeded into the bottom of the medium in each flask. Growth was much more abundant in the

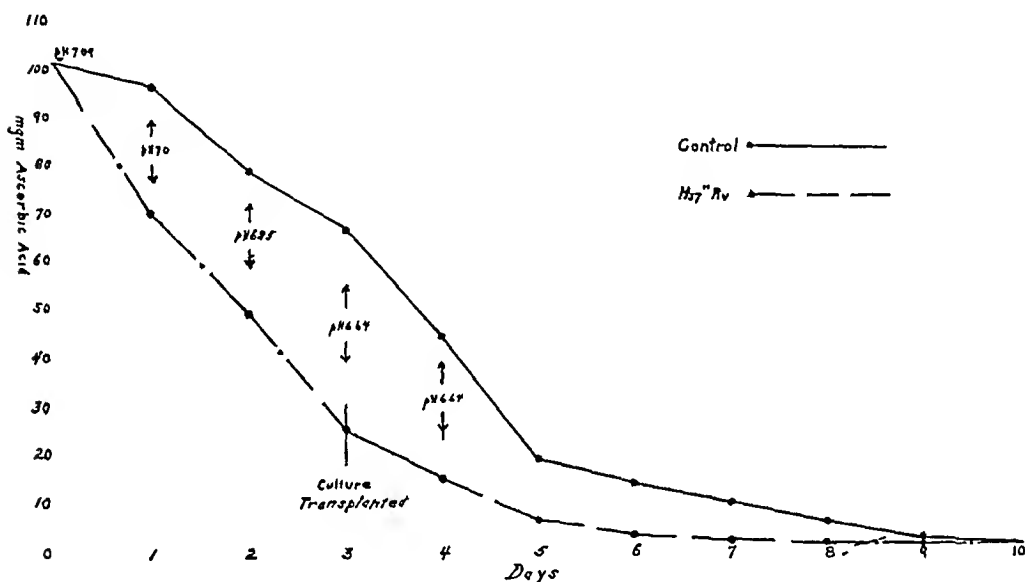


FIG 1

control flasks. Daily subcultures were made for the first four days and subsequently every third day for five weeks upon slants of Hohn's medium—pH 6.5. Abundant growth appeared on subcultures of the controls within eight days but the subcultures from the cevitic acid cultures developed only a few colonies and showed a growth lag three to five times as long as in the controls. After ten days growth developed more rapidly than previously in all cevitic acid cultures and in the subcultures. All transplants to Hohn's medium were further subcultured on the same medium to determine whether there were differences in growth characteristics. None was noted after 40 days.

VIRULENCE

Four guinea pigs were inoculated intratesticularly with some of the less typical deepseated growth from the cevitic acid flasks. All of the pigs reacted, intradermally, to 5 per cent O.T. two weeks after inoculation. Death from generalized tuberculosis occurred in all four pigs within 90

days Growing colonies from two of the Hohn's medium subcultures of the cevitic acid flasks were inoculated into guinea pigs The colonies were isolated and raised somewhat in structure About 30,000 bacilli, dry weight, from each of two colonies that had different structure than the parent colony were inoculated into two pigs These pigs were controlled with the inoculation of two pigs with a typical parent colony All four pigs reacted intradermally to 5 per cent O T two weeks after inoculation Death from generalized tuberculosis occurred also in these four pigs within 90 days

To discover whether the lag period noticed in the previous experiments was due to the reaction of the medium, another experiment was performed To each of two flasks containing 20 c c of synthetic medium, 100 mg of partially neutralized cevitic acid were added The flasks were incubated at 37.5° C for five days Small portions of the medium were removed for titration with sodium 2, 6-Dichloro-Benzenone-endo-3-chlorophenol (Eastman) from time to time and it was found that no unchanged cevitic acid remained after seven days The color of the medium was then a burgundy The contents of each flask were then neutralized with N/10 NaOH until the pH corresponded with that of the medium in two control flasks, viz, pH 7.2 H₃₇ Rv variant was floated on the surface of the medium in all four of the flasks, two containing reduced cevitic acid and two controls Growth was slower in the presence of reduced cevitic acid than on the controls Growth characteristics and microscopic morphology were the same in all flasks Animal inoculations were not made

The above experiment was repeated but instead of allowing the cevitic acid to become entirely changed, 100 mg of the partially neutralized acid were added to the two experimental flasks every third day (Previous determinations had shown the rate of change in the synthetic medium used, see table) Such additions were carried out for a period of nine days—a total of 300 mg At this time a marked difference in the growth characteristics was noted in the two cevitic acid flasks as compared to the controls Growth was denser and less spreading in the cevitic acid flasks It appeared as small raised islands with but little of the veil-like intervening growth which characterized that in the control flasks The cevitic acid medium growth resembled that of an Ra variant rather than an Rv variant Changes in the reaction of the medium* as noted in the table were too slight to have accounted for the variations in growth

The experiment of growing the bacilli in the constant presence of cevitic acid was carried out in another way The Rv variant was floated on the medium and then subcultured on similar medium every third day The controls were treated likewise Two thousand one hundred mg of cevitic acid were used Again the growth resembled that of an Ra rather than an Rv variant as appeared in the controls On the cevitic acid

*We are indebted to Dr Eric Alling for making pH determinations with a glass electrode

medium the growth appeared as an elevated island without a veil-like periphery, whereas on the controls the growth was flat, veil-like and extended up the sides of the flasks

VIRULENCE TESTS

Four guinea pigs were inoculated intracerebrally, two with approximately 2,500 organisms, dry weight, from the cevitic acid culture and two with the same dose from the control cultures. All four pigs reacted to 5 per cent O T intradermally two weeks after inoculation and died of tuberculosis of the brain within 34 days.

Six other pigs were inoculated subcutaneously with about 5,000 organisms, three from the cevitic acid cultures and three from the control flasks. No change in virulence was noted at autopsy.

SUMMARY

The addition of cevitic acid to Proskauer and Beck's synthetic medium alters the character of the growth of tubercle bacilli floated on it. On this medium Rv variants of the H₃₇ strain develop like Ra variants whereas in control broth without cevitic acid the growth retains its Rv characteristics. There is no associated alteration in the virulence of the organisms.

Note The cevitic acid used in these experiments was donated by Merck and Company, Rahway, N J.

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CASE REPORT

CONGENITAL DISPLACEMENT OF THE TRICUSPID VALVE (EBSTEIN'S DISEASE) REVIEW AND REPORT OF A CASE WITH ELECTROCARDIOGRAPHIC ABNORMALITIES AND DETAILED HISTOLOGIC STUDY OF THE CONDUCTION SYSTEM

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CONGENITAL anomalies of the tricuspid valve unassociated with other major cardiac malformations are rare. However, there may be atresia of the valve, with or without stenosis of the right venous ostium, only one or two leaflets, or as many as four, five or six leaflets, excessive development of the valve with atresia of one leaflet, an extra leaflet fused with one of the normal leaflets, congenital neoplastic hyperplasia of the valve, displacement of the valve downward into the right ventricle, or even transposition of the tricuspid and mitral valves. Herxheimer¹ (1909-1913) reviewed briefly the reported cases of such anomalies, which, of course, have been augmented since his study. In 1866 Ebstein² described the first definite case of congenital displacement of the tricuspid valve, and since that time at least 14 essentially similar cases have been recorded, making, with the new case described in this report, a total of 16 certain cases in the literature.

REVIEW OF THE LITERATURE

Ebstein's patient (1866) was a man of 19 years who had had dyspnea and palpitation of the heart since childhood. For two years before death he had had a productive cough. For 16 days before death he had presented symptoms and signs of heart failure with tricuspid regurgitation, as well as manifestations of tuberculous pneumonitis. The heart was greatly enlarged. There was a forceful pulsation and a thrill over the precordium. A long murmur, beginning in systole but running through diastole and obscuring the heart sounds, was heard best at the base of the heart, on the right side, and also in the back. The second pulmonic sound was not accentuated. At necropsy the right auricle was found to be hypertrophied and widely dilated. The Thebesian valve was absent. The foramen ovale was not completely closed and the flap contained several fenestrae, one quite large. In the large right ventricle was seen a large membrane springing from part of the annulus fibrosus, the anterior and posterior walls of the ventricle and partly in its posterior and inferior half from the interventricular septum. Its external and under surface was attached to the anterior and lower wall of the ventricle by chordae tendineae and papillary muscles. This repre-

* Presented at the St. Louis meeting of the American College of Physicians, April 23, 1937.

From the Georgetown University School of Medicine, the University of Minnesota School of Medicine, and the Army Medical Museum.

sented the fused and downwardly displaced anterior and posterior leaflets of the tricuspid valve. The membrane was white and glistening and fenestrated, especially in its lower half. These fenestra opened into a space between the outer surface of the membrane and the wall of the ventricle. About 15 mm below the annulus fibrosus a small flap arose from the endocardium of the interventricular septum with its base above and its apex below, whose edge was attached by chordae tendineae to the endocardium. This represented the isolated and malformed septal or medial leaflet of the tricuspid valve. It formed, with the anterior portion of the large membrane, an oval opening measuring 4 by 3 cm into the conus arteriosus. The right ventricle was greatly dilated. The left auricle and ventricle were normal. The malformation of the heart, therefore, consisted mainly of an anomalously formed and downwardly displaced tricuspid valve which divided the right side of the heart into a large auricular portion consisting of the true auricle and the greater part of the ventricle and a smaller ventricular portion consisting of the lower portion of the true ventricular cavity and the pulmonary conus. During ventricular systole part of the blood in the latter ventricular portion undoubtedly ejected blood both into the pulmonary artery and back into the auricular portion. Until the time of the terminal heart failure the excess blood in the auricular portion probably passed through the patent foramen ovale, thus preventing positive venous pulsation and passive congestion of the viscera. Ebstein explained the murmur as being due in its systolic component to blood rushing back into the right auricle and venae cavae and in its diastolic component to the blood streaming into the cavity of the ventricle over the surface of the not entirely smooth membrane. Besides the cardiac findings the necropsy revealed active and advanced pulmonary tuberculosis and congestion of the viscera.

Marxsen³ described the next case of this cardiac anomaly in 1886. The patient, a woman aged 61 years, developed profuse diarrhea with a high fever and rapid pulse rate after the extraction of a mature cataract. At necropsy the cardiac findings were apparently unexpected, and there was no passive congestion of the viscera. Death had been due to ulcerative colitis. The right side of the heart was very large, the left small. There was thickening of the mitral valve. The tricuspid valve was represented by a pouch-like membrane composed of three indistinctly differentiated and fused components. The membrane was attached to the wall of the ventricle much as in Ebstein's case, but the septal component was not isolated but was fused with the anterior component. The posterior component was attached vertically downward along the interventricular septum, the very large anterior component to the anterior wall of the ventricle. There were numerous small chordae tendineae holding the edges of the valve down to the wall of the ventricle and the moderator band without the intervention of true papillary muscles. The largest component was almost fused to the wall of the ventricle. The valve opened into the pulmonary conus through an aperture 3 cm in diameter. The foramen ovale was patent, and the Eustachian valve was well developed. The pulmonary conus was broad and hypertrophied.

MacCallum's⁴ case (1900) was similar. The patient was a man who had always been blue and who died at the age of 30 years of pulmonary tuberculosis. At the necropsy there was found chronic tuberculosis of the lungs and chronic passive congestion of the viscera. The heart was enlarged, especially the right side. The Eustachian valve was persistent as a large apparently functional

valve The valvula foraminis ovalis also persisted but was not competent to close the foramen ovale, which was open to a width of about 1 cm The very large appendix auriculæ opened by two mouths into the auricle which was somewhat constricted near its middle by a muscular ring The tricuspid valves were ballooned out into the right ventricle and had apparently become closely grown together with the ventricular wall Two of the segments were visible against the interventricular septum and toward the left as wrinkled, folded membranes, which were very soon fused with the ventricular wall and were apparently functionless The remaining membrane seemed to furnish the whole membrane which lined the ventricular wall and septum and which below, roofing the trabeculae, formed the floor of a sort of intervalvular chamber The latter opened into the ventricle through a round orifice situated toward the left just below the conus arteriosus and guarded by a flap-like fold of the chamber wall It further opened through several small fenestra, each guarded by tiny valves which were furnished with chordae tendineae and papillary muscles The pulmonary artery was slightly narrowed, and the ductus arteriosus persisted as a cord, but otherwise the heart was approximately normal

Schonenberger's⁵ case (1903) was that of a girl four and a half years old who was found to have cyanosis and clubbed fingers There was an intense thrill over the precordium, and systolic and diastolic murmurs replaced the heart sounds The area of cardiac dullness was greatly increased to the right, and bronchial breath sounds were heard over the right lung Death occurred suddenly At necropsy the heart was found to fill nearly the whole of the right hemithorax, and the right lung was thin, indurated and almost completely calcified The wall of the right ventricle appeared to be a thin membrane distended with blood The left ventricle was very small with firm thick walls, a thickened endocardium and numerous chordae tendineae between the papillary muscles The pulmonary artery was small compared to the aorta The auricles were very large A large membrane resembling a sail hung down in the right ventricle as in Ebstein's case and apparently represented the fused anterior and posterior components of the tricuspid valve There was an exaggerated moderator band between the conus arteriosus and the remainder of the right ventricle from which arose a papillary muscle with chordae tendineae attached to the large membrane and to the upper part of the conus arteriosus near the pulmonary valve Other papillary muscles existed lower down in the right ventricle with chordae tendineae attached to the membrane A smaller independent leaflet was attached to the septum, probably representing as in Ebstein's case the septal leaflet of the tricuspid valve There was an oval opening into the conus arteriosus between the membrane and the moderator band, and small fenestra also existed in the membrane near its edge where it was attached to the chordae and papillary muscles The large auricular portion of the right ventricle was very thin-walled and contained almost no muscle tissue The foramen ovale was wide open Eustachian and Thebesian valves persisted

Geipel⁶ (1903) reported three cases of Ebstein's disease The first was that of a museum specimen of a male aged 18 years, the second was also that of a museum specimen, and the third was that of a male aged 15 years who for three months had had edema of the legs and extreme weakness This patient had some cyanosis, the heart was enlarged to left and right, there was gallop rhythm, and the heart sounds were weak and diffuse There were pulmonary

riales Just before death thrombosis occurred in the left femoral vein and the right jugular vein, and an embolus lodged in the Sylvian artery. In all three cases there was great enlargement of the right side of the heart. In the place of the normal tricuspid valve a broad band or a sack hung far down into the right ventricle, as in the cases previously described. The anterior leaflet was the best developed in all three cases, and it fused with the somewhat less well developed posterior leaflet. The septal leaflet was the most poorly developed. The orifice into the conus formed by the free edge of the anterior leaflet, the septal leaflet and the prominent moderator band was triangular or oval. In case 3 it was multilocular due to excessive development of muscular elements in conjunction with the valve. In case 1 papillary muscles were either completely lacking or were very rudimentary. Numerous chordae tendineae were present in all three cases, either in groups or discrete, they were longest on the anterior leaflet, so that that leaflet, the largest, was most free. The septal leaflet was practically devoid of chordae. The foramen ovale was patent or fenestrated in each case, but the left auricle was not enlarged in any. Geipel called attention to a case described by Riecke⁷ in 1831 which he considered to be the first recorded case of this anomaly of the tricuspid valve, but while there are certain resemblances it is certainly not the same malformation. In Riecke's case there were major defects of the right auricle, the tricuspid valve was absent, and some muscular trabeculae (but not a valve) divided the right ventricle into two cavities.

Malan's⁸ case (1908) was that of a 60 year old man who had presented manifestations of heart trouble for two years before death. The heart was moderately enlarged, and there was a loud systolic murmur. The liver was enlarged, and slight edema was noted. At the necropsy numerous splenic infarcts and thrombosis of the right iliac and the mesenteric artery were found. The left ventricle was hypertrophied and fibrotic. The right auricle and ventricle were enlarged. The tricuspid valve stretched downward toward the apex. The anterior component was large and attached partly to the annulus fibrosus and partly to the anterior wall of the ventricle. The other two leaflets were small and attached to the interventricular septum. The passage between the auricular portion of the right heart and the conus arteriosus was formed by the wall of the ventricle and the anterior leaflet. The valve was attached to the myocardium directly by means of chordae tendineae. A large Eustachian valve was present.

Heigel⁹ (1913) also reported three cases of this congenital anomaly. The first case was that of a girl of 10 years who had always been well until a week before death, when she vomited, became apathetic and complained of substernal pain and then became somnolent with a pulse rate of 56 per minute. An early systolic murmur was noted. There was a little cyanosis. Necropsy showed an early cerebral abscess with a localized purulent meningitis. The liver was congested. The right auricle and especially the right ventricle were enlarged, the latter being three times as large as the left ventricle and giving the impression of a thin-walled sac. The foramen ovale was wide open, and the Eustachian and Thebesian valves were well developed. In place of a normal tricuspid valve there was a broad connective tissue septum which was attached to part of the annulus fibrosus and to the anterior wall of the right ventricle down as far as the apex and to the interventricular septum in its lower part. This had a large anterior and a smaller posterior component with an opening between, from the edge of which short chordae tendineae passed to a small papillary muscle in the

conus arteriosus and to the moderator band. A slit-like opening into the conus was formed by the thickened free edge of the anterior component and the upper part of the interventricular septum. The lower free edge of the anterior component was attached by chordae tendineae to another small papillary muscle in the conus. A small remnant of a septal leaflet was attached to the upper part of the interventricular septum, and in the septum below this there was a large thickened plaque in the endocardium. The left auricle was not enlarged. The posterior leaflet of the mitral valve was divided by a cleft into two equal parts. There was some thickening of the free edges of the mitral valve and some of the chordae tendineae. There were two small areas of thickening of the left auricular endocardium.

Heigel's⁹ second case was a case previously studied by Verocay in 1907. The patient was a girl, aged 3 years, with cyanosis and clubbed fingers and toes, who died of measles with bronchopneumonia. She had been thought to have pulmonic stenosis. The heart was very similar to that of the first case, but papillary muscles and trabeculae were absent or very rudimentary, and the mitral valve was not abnormal. The foramen ovale was open.

Heigel's⁹ third case was that of a museum specimen of 1855 which Tietz had studied. The patient was a woman aged 38 years who died of "paralysis cordis." The right heart was quite similar to those of the two previous cases, but the anomalous tricuspid valve was thicker and roughened and was attached directly to papillary muscles without chordae tendineae. Also, the foramen ovale was closed and the auricular portion of the right ventricle was not so large. The right auricle and left ventricle were dilated, and in the left ventricle below the aortic valve and on the membranous septum there was a large thickened plaque.

Blackhall-Morison and Shaw¹⁰ (1919) reported the case of a man of 38 who had had "heart trouble" for three years and who died of pulmonary and meningeal tuberculosis. There had been marked accentuation of the first heart sound and a precordial systolic bruit. The right auricle and ventricle were both dilated and hypertrophied. The columnae carneae were decidedly hypertrophied and especially one running downward and outward from the base of the posterior cusp of the pulmonic valve. The tricuspid orifice was dilated. The septal leaflet of the tricuspid valve was "fleshy" and "sessile." The anterior leaflet was redundant and attached in its normal position. The posterior leaflet coalesced at its right boundary with the right limit of the anterior cusp but was attached abnormally low in the ventricle, and its left portion was divided into two parts. A large, tough umbrella-like flap was attached to the ventricle close to its apex, and a second smaller portion was 'fleshy' and "sessile." The foramen ovale was closed, and there was a well developed Thebesian valve. There was also congenital absence of one kidney with abnormal development of the ureter on the same side.

Blackhall-Morison¹¹ later (1922) reported the case of a man of 33 years who had been known to have heart trouble since the age of 21 years and who died suddenly. The heart was a typical specimen of Ebstein's disease. The right heart was much dilated and its wall very thin. The auriculoventricular orifice admitted the whole hand. The largest leaflet of the valve was the anterior, and the septal leaflet was small and attached vertically to the septum. There were two large papillary muscles. The membranous portion of the interventricular septum was abnormally large. The foramen ovale was closed.

Ainstein's¹² case (1927) differed from those previously described mainly in that the posterior leaflet of the tricuspid valve was the largest. The anterior leaflet was thick and suggested a triapeze. Both anterior and posterior leaflets were attached largely to the papillary muscles directly. The medial leaflet was attached directly at its free edge to the septum by short, delicate chordae tendineae. All three leaflets were joined together, the medial one not being independent as in some of the other cases described. There were two openings into the conus arteriosus, a smaller medial one and a larger lateral one. In the wall of the auricular portion of the ventricle the myocardium was practically absent. The pulmonary valves were thin but somewhat grown together, with slight stenosis. The foramen ovale was open, and the Eustachian and Thebesian valves were well developed. The patient was a woman of 20 who had had cyanosis of the lips, nose, ears and fingers since early childhood, with palpitation and dyspnea on exertion and latterly pressing pain over the sternum. Clubbing of the fingers had existed since the age of 14 years, and the patient had never menstruated. She developed symptoms and physical signs of advanced pulmonary tuberculosis, which caused death. The heart was moderately enlarged, and there was a systolic-diastolic thrill over its left side. Over the middle of the sternum a long diastolic murmur was heard, while at the apex and the tricuspid area there was a loud, long systolic murmur and a short diastolic murmur. The cervical veins were distended but not pulsating, the liver was neither enlarged nor pulsating. Toward the end edema appeared, but the cyanosis became less intense.

Finally, the case of Bassen described briefly by Abbott¹³ (1928) was that of a lad of 16 who died of erysipelas. He had had palpitation of the heart and dyspnea for several years and for two years precordial pain, some edema of the legs, and cyanosis of the lips and nailbeds. There was a very wide area of cardiac impulse with great enlargement of the heart to the left, and there were systolic and diastolic thrills at the apex, and systolic murmurs were heard over the entire precordium. At necropsy chronic passive congestion of the viscera and congenital absence of the left kidney and ureter were found. The heart was greatly enlarged, due mainly to a much dilated right auricle, and the right cardiac chambers had extremely thin walls. The tricuspid valve was absent from its usual site, but near the apex of the right ventricle there was a membranous leaflet with a stenosed multilocular orifice leading into a small ventricular cavity communicating directly with the pulmonary artery. This membrane was attached to numerous papillary muscles by "uneven" chordae tendineae. The foramen ovale was widely patent. The left ventricle was slightly dilated and hypertrophied. The mitral valve was slightly thickened along the line of closure. This was undoubtedly a case of Ebstein's disease with definite tricuspid stenosis as well as regurgitation.

CASE REPORT *

Clinical Course The patient was a white woman, aged 21 years at the time of her death. On October 4, 1930, at the age of 15 years she had first been examined at the Lymanhurst School Heart Clinic of Minneapolis, at which time she had stated that a diagnosis of heart disease had been made when she was 7 years old. There was no history of rheumatic infection. She had no complaints, and her general condition was good. She was a well developed, well nourished school girl. There was no cyanosis or clubbing of the fingers. The heart was enlarged both to the right

* Army Medical Museum Accession No. 50981

and the left. The heart sounds were slow and regular. A harsh, blowing systolic murmur was heard along the left border of the sternum, with maximum intensity in the third left interspace. This murmur replaced almost the entire heart cycle and suggested a congenital lesion, but there was no thrill. The second pulmonic sound was somewhat accentuated. Roentgenographic examination revealed marked cardiac enlargement, and a lateral film made with the esophagus filled with barium showed definite posterior displacement of the esophagus. The transverse thoracic diameter was 24.0 cm, and the total transverse diameter of the heart was 15.0 cm, with M L measuring 9.2 cm and M R, 5.8 cm.

The patient was not seen again until January 11, 1933. She still had no complaints and looked very well. The heart was essentially the same except for the presence of frequent premature contractions. The vital capacity was 1500 cc.

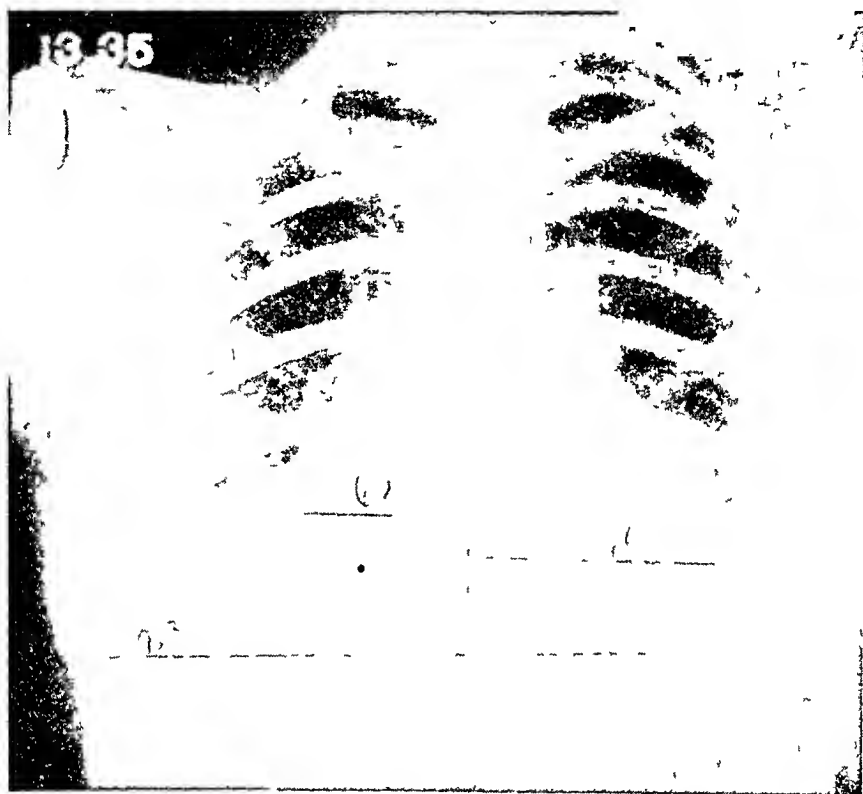


FIG 1 Enlarged heart, especially toward the right

Roentgen-ray examination revealed the same marked cardiac enlargement, with the measurements all slightly greater than before.

When examined again on March 31, 1934 she was well except for some dyspnea. The hands were now cold, clammy and cyanotic, and there was a suggestion of clubbing of the fingers. The vital capacity was 1420 cc.

On March 13, 1935 the findings were essentially the same, but cyanosis and clubbing of the fingers were not definite. There were numerous premature beats. The long, harsh murmur was best heard in the fourth interspace just to the left of the sternum and seemed to occupy the entire heart cycle. It was fairly well transmitted toward the apex but was not heard beyond the precordium nor in the neck. The second pulmonic sound was not audible. The blood pressure was 104 systolic and 90 diastolic. The roentgenogram showed the heart to be considerably enlarged to both sides (figure 1). There was no enlargement in the region of the superior or

median convexities, and although the enlargement in the region of the right auricle was most marked and unusual the contour of the heart could not be said to be typical of any lesion. The transverse thoracic diameter was 25.3 cm, the total transverse diameter of the heart was 15.8 cm, with M-L measuring 9.6 cm and M-R, 6.2 cm. The vital capacity was only 1000 cc. The electrocardiogram showed left axis deviation, rate 72, PR interval 0.16 sec, occasional ventricular premature beats, QRS 0.16 sec in Leads I and II, and 0.12 sec in Lead III, P-wave positive in all leads, T-waves in Lead I variable and either positive or negative (figure 2). The second lead was most interesting in that it showed changes in the shape of the main ventricular complexes, suggesting that the excitation wave was taking different directions at different times.

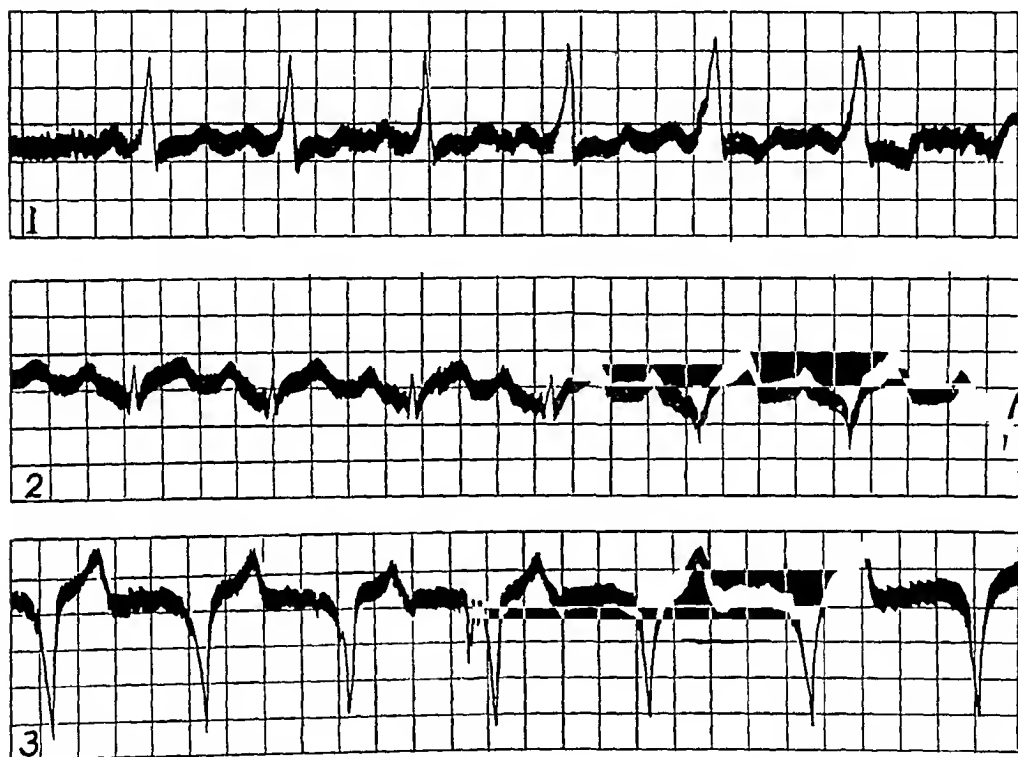


FIG 2 Conventional three leads left axis deviation, prolonged QRS complexes, variation in form of ventricular complexes, Lead II

The patient attended a dance on the night of June 29, 1936 and was apparently in her usual good health when she retired at 10 p.m. Her parents were awakened by a noise in her room at about 2 a.m. the same night and upon investigation found her to be dead in bed.

Necropsy Necropsy was performed at 9:30 a.m., June 30, 1936, by Dr. J. S. McCartney of the University of Minnesota School of Medicine. There was no cyanosis or edema. Except for the heart there was little to be found besides intense acute congestion of the spleen which weighed 275 gm, of the liver which weighed 1525 gm, and of the kidneys which were not enlarged. The lungs presented no evidence of congestion or edema.

Gross Description of the Heart The pericardial sac measured 15 cm in its transverse diameter. The heart appeared to be enormous. When emptied of blood it weighed, however, only 275 gm. Even upon superficial inspection it was evident

that the great size of the organ was due to tremendous dilatation of its right chambers. Externally the right ventricle appeared to be moderately enlarged, but what seemed to be the right auricle was a very dilated, thin-walled chamber which obviously encroached upon the right ventricle. Its inferior and posterior walls were especially thin. The venae cavae were in their normal positions with respect to the right auricle, which formed the right one-third of the anterior surface of the heart, the pad of fat about 3.5 cm in diameter and about 1.0 cm in its thickest part. The left ventricle and auricle were both relatively small, and the former occupied very little of the anterior surface of the heart and practically none of the apical portion. The mouths of the pulmonary veins were not present in the specimen after removal from the body, but it was certain that they occupied their usual position. The aorta and pulmonary artery were joined with their proper ventricle and were in normal relation to each other. The auricular appendages were in their normal positions.

After opening the heart in the usual manner it was seen that both the right auricle and ventricle, especially the former, were greatly dilated and that the tricuspid valve was displaced and malformed. The left auricle and ventricle were comparatively small but appeared normal. The two coronary arteries, which were pliable and smooth-walled, had their usual origin. The circumflex branch of the right passed obliquely downward and toward the right on the anterior surface of the heart and then toward the left to the very inferior edge of the heart, forming a semicircle. This apparently anomalous location was due to the great enlargement of the right auricle, which formed the right one-third of the anterior surface of the heart, the vessel was actually in its normal location in relation to the right auricle and ventricle. The left coronary artery divided as usual into the anterior interventricular artery and the left circumflex artery. The latter ended in two large branches, one on the lateral wall of the left ventricle which ran obliquely anteriorly and downward from the posterior junction of the auricles and the ventricles, and another which ran downward from this point toward the lower edge of the heart on the posterior wall of the right ventricle and apparently represented the posterior interventricular artery, although it did not lie in the posterior interventricular sulcus.

The aortic valve appeared normal and measured approximately 5.0 cm in circumference. The membranous portion of the interventricular septum was quite small, the muscular portion reaching almost up to the base of the aortic valve. The mitral valve had its normal structure and its normal chordae tendineae and papillary muscles. The mitral orifice was about 9.0 cm in circumference. The thickness of the left ventricle near its base was 1.0 cm. The depth of this ventricle was 7.0 cm. The endocardium of the left auricle and ventricle appeared normal, as did their musculature.

The right side of the heart presented a very anomalous appearance and was a typical example of Ebstein's disease (figures 3 and 4). By far its greater part functioned as the auricle, since the tricuspid valve was displaced down into the ventricle, its line of attachment passing around the wall of the ventricle in a vertical direction instead of transversely between the auricle and the ventricle, dividing the ventricle into a proximal auricular two-thirds and a distal one-third which functioned as a ventricle. However, the true auricle and ventricle were joined as normally at the annulus fibrosus, which ran transversely, and the true auriculoventricular orifice was wide open and actually dilated. There was a very definite Eustachian valve in its normal location, and the coronary sinus was in its normal situation below this, although it did not have a Thebesian valve. The fossa ovalis was at its normal site but was patent, there was a thick fold in the left auricle across the foramen ovale, which was open at the top. This fold apparently made closure of the foramen fairly competent except for a small fenestrum in the lower part of the fold. The pectinate muscles of the right auricle were normal and had their origin at the annulus fibrosus.

The auricle bulged far out and its wall was translucent and composed almost entirely of connective tissue. The central fibrous body was in its normal position.

The anterior papillary muscle of the right ventricle was displaced from its usual site downward and forward toward the very apex and lay in the functional right ventricle beneath the displaced tricuspid valve. The tricuspid valve formed a

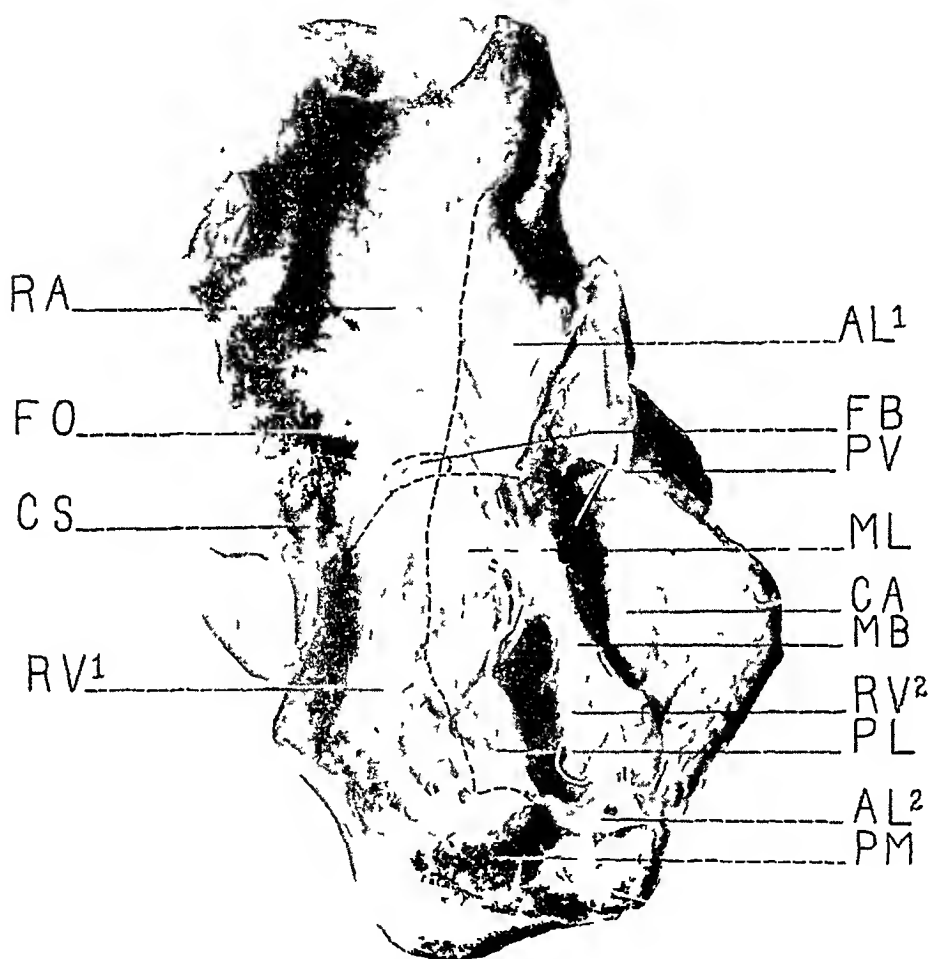


FIG 3 Open right auricle and ventricle. RA, true right auricle, FO, foramen ovale, CS, coronary sinus orifice, RV¹, auricular portion of right ventricle, AL¹, anterior leaflet of tricuspid valve (main portion), FB, central fibrous body (oval in broken line), PV, pulmonary valve, ML, medial leaflet of tricuspid valve, CA, conus arteriosus, MB, moderator band, RV², functional right ventricle, PL, posterior leaflet of tricuspid valve, AL², anterior leaflet of tricuspid valve (lower end), PM, papillary muscle (not visible). Vertical broken line indicates line of attachment of tricuspid valve, horizontal broken line indicates true auriculoventricular junction.

continuous fold around the interior of the right ventricle and could be divided only arbitrarily into three leaflets. The septal or medial leaflet was attached vertically to the upper half of the interventricular septum below and anterior to the central fibrous body. It had short broad chordae tendineae passing forward into the prominent moderator band. This leaflet passed downward to fuse without a definite line

of demarcation into the much dislocated posterior leaflet, the free edge of which was rounded and thickened but not apparently diseased. It was about 1.5 cm wide, and its attachment was vertically downward along the middle of the interventricular septum toward the apex. On its septal surface it was attached to a small teat-like papillary muscle, and at its lower extremity it was attached directly on its under surface to the papillary muscle in the apical region of the ventricle already referred to. Near the apex it fused with the larger anterior leaflet. The latter was attached at its upper limit to the annulus fibrosus and anterior upper limit of the interventricular septum, being fused with the medial leaflet where one stout chorda tendinea also attached it to the upper portion of the moderator band. Its line of attachment

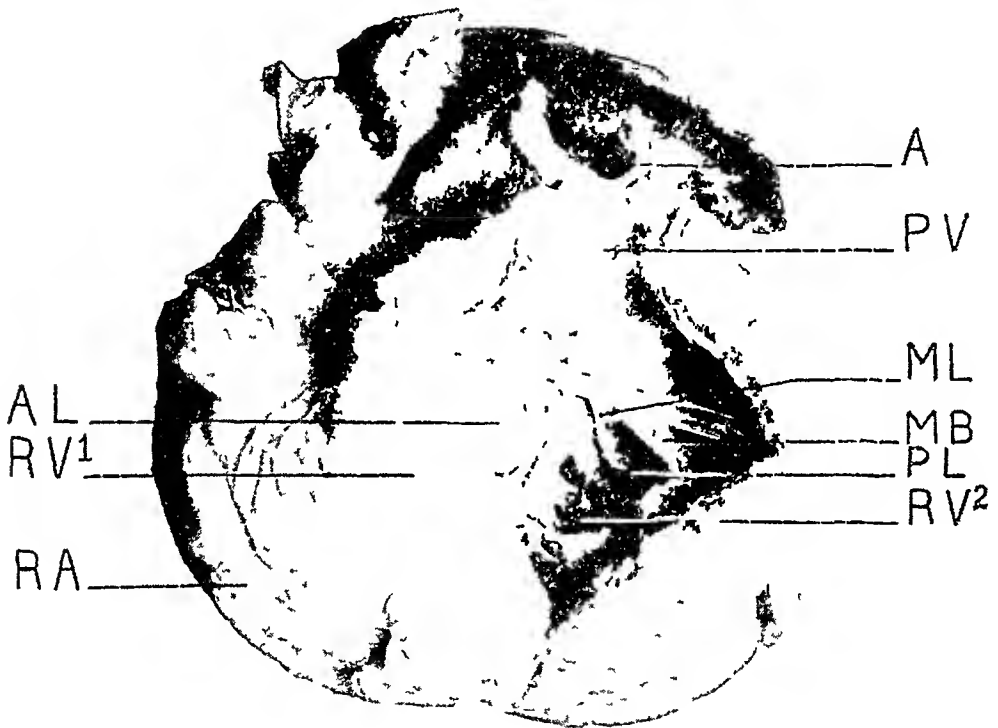


FIG 4 Anterior view of right auricle and ventricle held open at anterior incision, looking into functional right ventricle, RV², and conus arteriosus to right of moderator band, MB. A, aorta, PV, pulmonary valve, ML, medial leaflet of tricuspid valve, PL, posterior leaflet of tricuspid valve, AL, anterior leaflet of tricuspid valve, RV¹, exterior of auricular portion of right ventricle, RA, exterior of lower portion of enlarged right auricle.

then passed down the anterior wall of the ventricle toward the apex where it fused with the posterior leaflet. It was roughly triangular and about 2.5 cm wide in its widest portion. Its free edge was rounded and thickened like that of the posterior leaflet. It had a few delicate chordae tendineae attached to the under surface of its apical portion which fixed it lightly to the apical part of the ventricle, but its main attachment there was directly to the papillary muscle. The line of attachment of the whole valve measured about 1.20 cm.

The moderator band ran obliquely downward and forward from below the central fibrous body between the conus arteriosus and the small part of the right ventricle below and anterior to the displaced tricuspid valve. It formed a muscle

septum dividing the conus arteriosus from the functional right ventricle and was attached to the anterior part of the interventricular septum and the anterior wall of the conus. In its upper portion it was merely a trabeculum protruding from the interventricular septum, but in its lower half it was very broad, fan-shaped and thinner, and projected far out into the ventricular cavity and the conus.

The apical region of the ventricle beneath the tricuspid valve was a small chamber divided into two parts by the papillary muscle and a small muscular trabeculum joined to it. These spaces communicated with the small portion of ventricle between the valve and the broad moderator band by means of a cleft.

Histologic Study of the Heart Two large blocks of tissue were excised from the heart which included most of the auriculoventricular septum and all of the interventricular septum. These blocks were imbedded in paraffin, and serial sections of 10 microns thickness were cut horizontally from above downward. All sections were mounted, and every fifth section down to section 670 of block 1 and every tenth section beyond that was stained with Masson's trichrome stain. There were 2820 sections made from block 1 and 1680 from block 2, making a total of 4500 sections. The auriculoventricular node and bundle were quite normal in structure and in their relationship to the true right auricle and the central fibrous body (figure 5). The division of the bundle of His into its two branches began at about section 490. On the right side of the interventricular septum the tricuspid valve was seen to be attached to the right of the middle in a vertical direction from above downward. The moderator band became more and more prominent as the sections descended, until in the lower part of block 1 it formed a high, moderately thin projecting muscular band at the anterior edge of the septum. The right bundle branch, normal in structure throughout its course, ran at first directly beneath the line of attachment of the septal leaflet of the tricuspid valve in a rather prominent small projection, surrounded on its peripheral and lateral sides by a fibrous rim and deeply by the septal musculature (figure 6). It changed in shape in its transverse section as it descended, becoming first fusiform, then roughly triangular and then oval. It gradually moved anteriorly from the middle of the septum, leaving the projection mentioned at about section 800 and moving toward the base of the moderator band which it reached at section 1060. It was subendocardial in this migration. The right bundle branch then gradually ascended along the posterior edge of the moderator band, lying beneath the anterior attachment of the septal leaflet as it ascended. The branch then gradually passed up to the unprotected summit of the moderator band which it reached at about section 2500, becoming a little deeper with a small rim of myocardium between it and the endocardium (figure 7). Below the middle of the interventricular septum in block 2 the moderator band became divided gradually from summit to base by a cleft, and the right bundle branch gave components to the two parts, spreading out broadly beneath the endocardium along the adjacent sides of the cleft and finally in the upper third of the block losing its identity (figure 8). The trabeculae carrying the bundle branch were at the base of the fan-like expansion of the moderator band.

The left bundle branch appeared quite normal in structure and location throughout its course beneath the endocardium covering the left side of the interventricular septum (figures 5, 6, 7 and 8). It gradually spread out to become broader and broader. About the middle of the septum it became definitely thicker in parts and began to divide into anterior and posterior divisions, which passed down toward the base of the anterior and posterior papillary muscles respectively and finally lost their identity in the lower part of the septum.

The endocardium and myocardium presented no evidence of ancient or recent inflammation, except for a small mass of fibrous tissue in the myocardium at about the middle of the septum and near its right ventricular surface, and changes in the wall of a moderately large intraseptal artery in the same general locality. These changes were suggestive of, but not pathognomonic of ancient rheumatic arthritis. Practically all other arteries appeared quite normal.

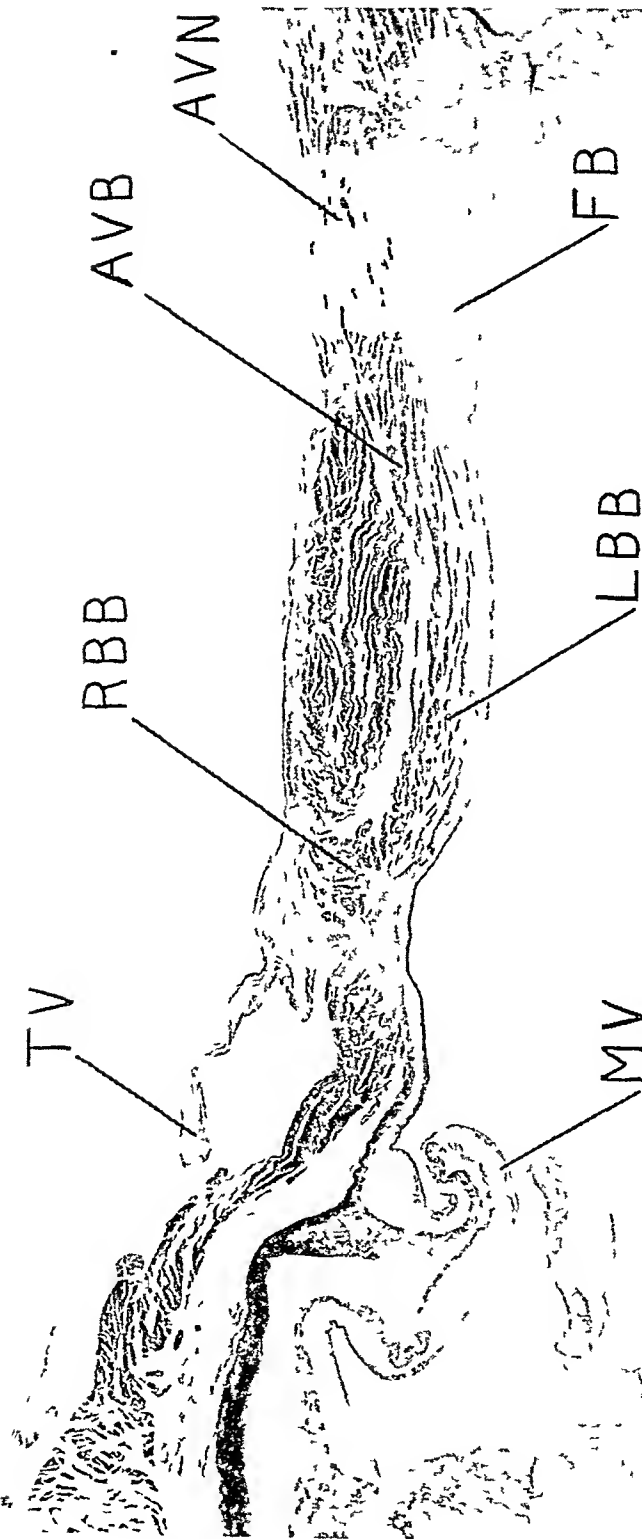


Fig 5 Horizontal cross section of upper portion of interventricular septum (block 1, section 485) TV, tricuspid valve (medial leaflet), RBB, beginning of right bundle branch, AVB, auriculoventricular node, AVN, auriculoventricular node, MV, mitral valve, LBB, beginning of left bundle branch, FB, central fibrous body Reduced from a magnification of 10 times

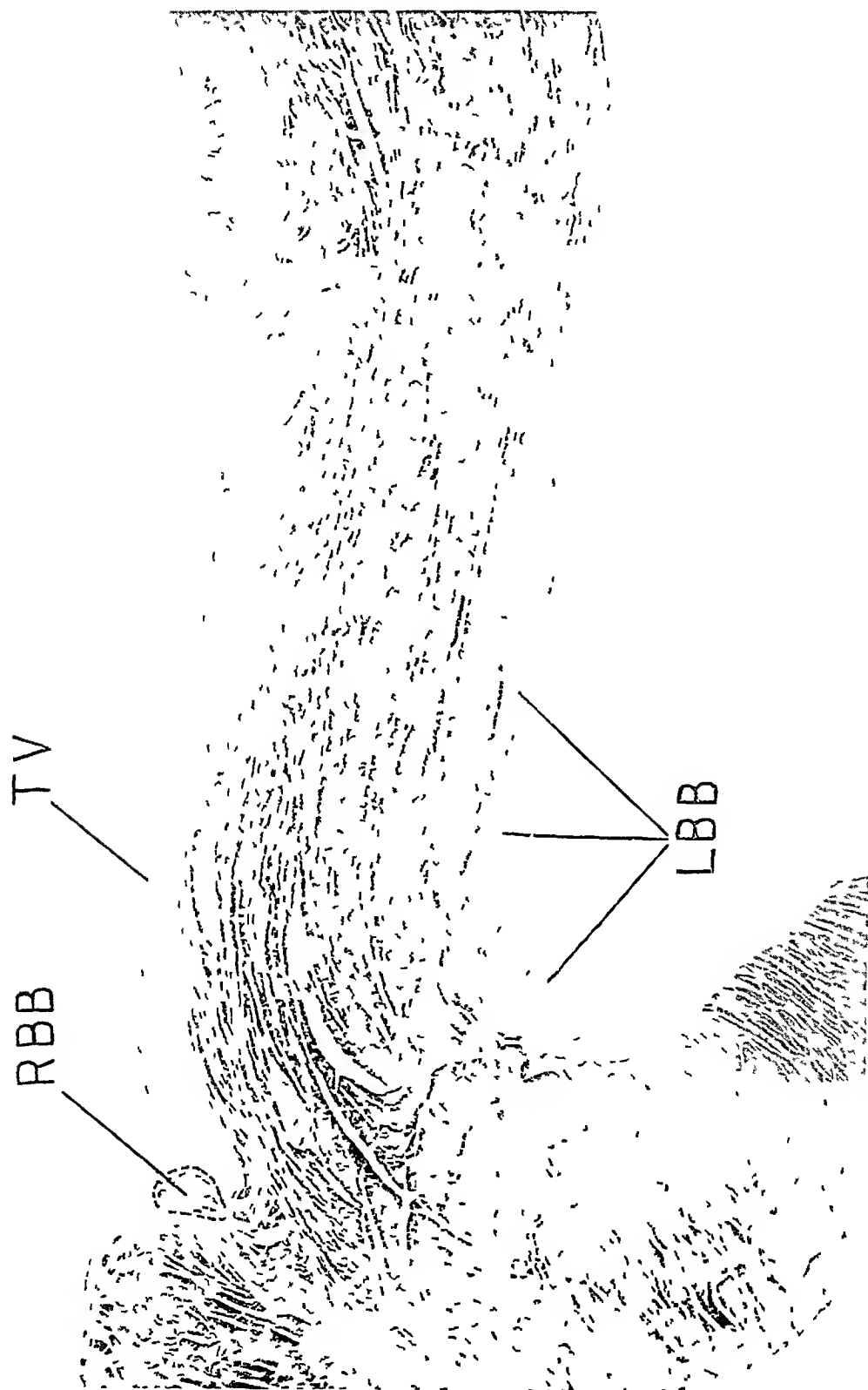


FIG 6 Horizontal cross section of interventricular septum, upper third (block 1, section 1470) RBB, right bundle branch, TV, tricuspid valve (medial leaflet), LBB, left bundle branch. Reduced from a magnification of 10 times

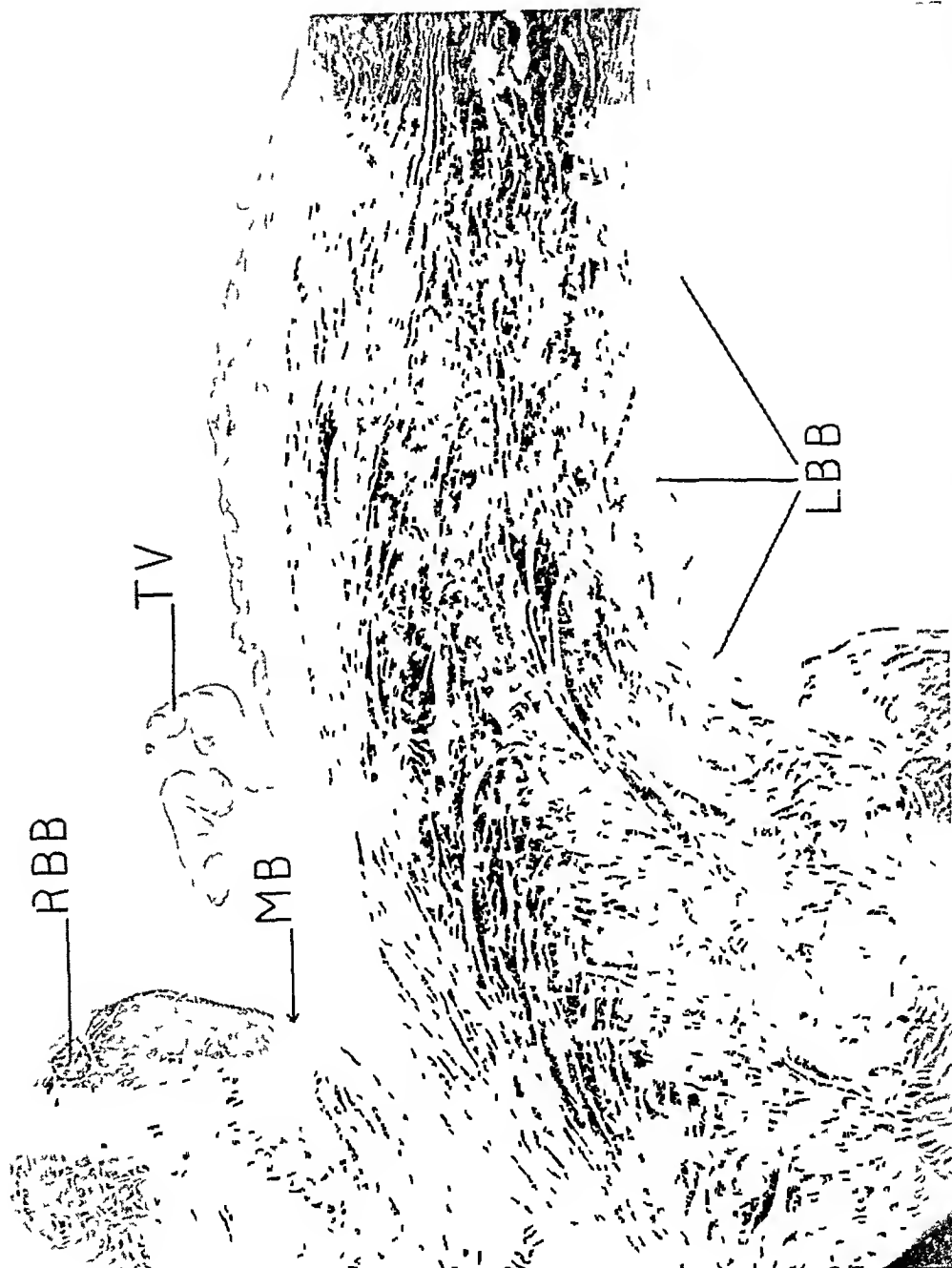


FIG 7 Horizontal cross section of interventricular septum, about middle (block 1, section 2430) RBB, right bundle branch, MB, moderator band, TV, tricuspid valve (posterior leaflet), LBB, left bundle branch. Reduced from a magnification of 10 times

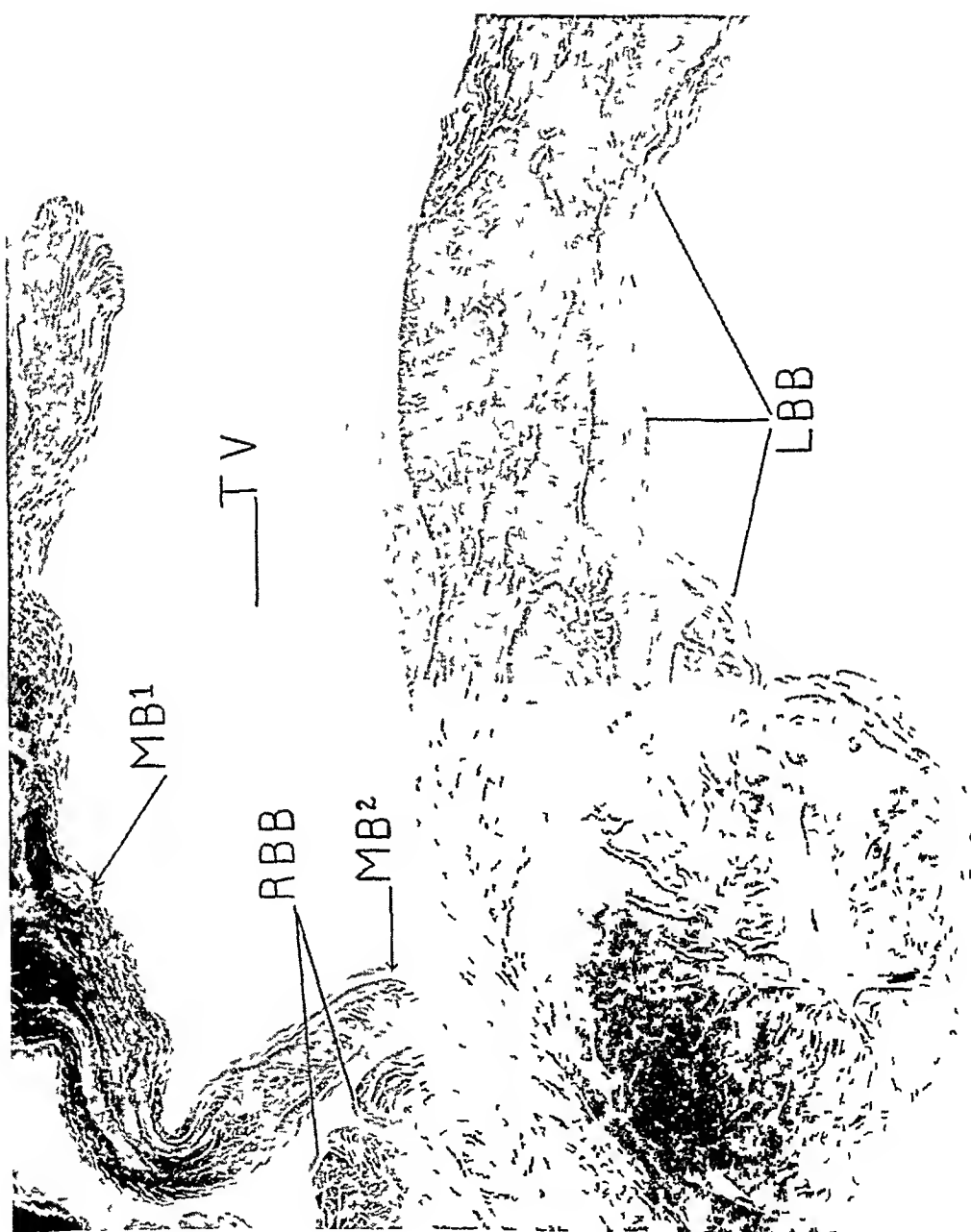


FIG 8 Horizontal cross section of interventricular septum, lower middle third (block 2, section 310) MB₁, fan-like broadening of moderator band, RBB, right bundle branch, terminal expanded portion, MB₂, true moderator band, TV, tricuspid valve (posterior leaflet), LBB, left bundle branch. Reduced from a magnification of 10 times

DISCUSSION OF CASE

The case was a typical example of Ebstein's disease. Congenital heart disease was diagnosed, but the type of malformation could not be determined before death. The electrocardiographic abnormalities suggested left bundle-branch block (new terminology), and it had been hoped that the histologic study would show definite evidence that would aid in settling the controversy now waging concerning the terminology of intraventricular block. However, the left bundle branch was entirely normal, and although the course of the right bundle branch was somewhat abnormal it conformed in a general way to that of the normal heart, and the branch was not interrupted at any part of its microscopically recognizable portion. One must conclude, therefore, that the electrocardiogram can not definitely be designated as that of bundle-branch block but rather of left axis deviation due perhaps to an electrical imbalance between the right and left ventricles associated with prolongation of intraventricular conduction time.

Of the cases described in the literature this case seemed to resemble most closely that of Arnstein. The components of the three leaflets were fused and continuous, and it was impossible to say exactly what their limits were. The valve was obviously incompetent, and tricuspid regurgitation must have occurred. However, the extracardiac signs of this dysfunction were lacking because of hemodynamic properties which will be discussed later.

COMPARISON OF CASES

The 16 cases of Ebstein's disease were similar in their fundamental nature, namely, the displacement of the valve downward into the right ventricle. In all, the anterior leaflet was partly attached to the annulus fibrosus, whereas the posterior leaflet had usually very little connection with it, and the medial or septal leaflet was attached to it in some cases and not in others. In almost all of the cases the anterior leaflet was much larger than the other leaflets. In some cases the septal leaflet appeared as an isolated, almost functionless flap attached to the interventricular septum, and in others it was an integral part of the whole valve. In some, the valve resembled a flapping sail, whereas in others, as in our case, it did not give that impression because the leaflets, especially the anterior, were either not so large or were more closely held by chordae tendineae and papillary muscles to the ventricular wall. There was considerable variation in the number, size and position of the papillary muscles and chordae tendineae. In some there were both present, in others there were mainly only papillary muscles or only chordae. The so-called moderator band, which in the human heart is usually poorly developed, was frequently much enlarged.

The amount of the ventricular cavity proximal and distal to the valve varied, but the distal portion was usually much smaller than the proximal, a condition which was exaggerated by the usually great dilatation of the so-called auricular portion of the ventricle. The degree of dilatation proximal to the valve, as well as the thinness of the wall, was apparently determined by the amount of regurgitating blood and possibly by the length of life. In all of the cases the true auriculoventricular ostium was enlarged, but there was considerable variation in the position, form and size of the actual valvular orifice between the auricular portion of the ventricle and the remainder of the ventricle, which consisted

mainly of the conus arteriosus. In all of the cases it appeared probable that the valve was incompetent to close its orifice completely, thus allowing regurgitation. In one case, at least, there was also definite stenosis of the orifice. There was considerable variation in regard to accessory fenestria of the leaflets. The pulmonary conus varied moderately in size and in the thickness of its wall, and there were also variations of a relatively minor nature in the pulmonic valve.

Associated cardiac anomalies were of minor nature. The most common and most important was the patency of the foramen ovale, but this was not present in all cases. It was undoubtedly secondary to the increased pressure in the right auricle. The amount of blood flowing through it into the left auricle was not sufficient in most cases to cause appreciable enlargement of that chamber, since there was probably a diminished amount of blood flowing into the left auricle from the pulmonary circulation. There was considerable variation in the Eustachian and Thebesian valves, and when well developed they were probably of some importance in preventing the back flow of blood into the venae cavae and the coronary sinus.

The split posterior mitral leaflet in one case was of interest, but only as an associated anomaly.

The thickened endocardial plaques and the thickenings of valve leaflets and chordae tendineae in a few of the cases were probably only incidental.

EXPLANATION OF THE ANOMALY

Opinions have varied as to the cause of the anomaly. A few authors have attached great importance to intra-uterine endocarditis, but this, when it occurs, is probably only incidental and due to the predisposition of such malformed parts to inflammation. The most plausible explanation seems to be that of MacCallum,⁴ who states: "The valves are, of course, formed on the medial side by a prolongation of the septum intermedium, on the lateral side by an involution of the wall of the auricular canal. If in an early stage these endothelial cushions reach a greater extent than normal and retain their attachment to the muscular trabeculae, they would in time become a membrane, supported by muscular trabeculae. This might occur only on the lateral side, the valves produced from the septum developing in part normally. The free edge has possibly lost its muscular attachment as a result of the inefficiency of muscular action in the direction in which the blood stream affects it."

The malformation occurs only in the otherwise essentially completely developed heart and probably before the eighth week of fetal life. According to Mall the posterior leaflet develops independently from the posterior wall of the endothelial tube, while the others originate from the endothelial cushions. In Ebstein's disease the posterior leaflet is the most anomalous, while the medial leaflet, though deformed, has always the most normal parts. Heigel believes that the usual large size of the anterior leaflet may be due to a compensatory effort.

CLINICAL FEATURES

It would appear to be impossible to make the diagnosis of Ebstein's disease during life. The type of enlargement of the heart is not characteristic. There

may be both systolic and diastolic murmurs, with or without a thrill, but more often there is only a long, loud systolic murmur of greatest intensity in the third and fourth intercostal spaces close to the left border of the sternum. The pulmonic second sound is usually not accentuated.

Cyanosis and clubbing of the fingers may or may not be present. The presence of cyanosis depends, of course, upon the amount of venous blood flowing into the left auricle through the foramen ovale and the degree of diminution of the flow of blood into the pulmonary artery. The amount of cyanosis in one case decreased near the end of life, probably because the failing right ventricle ejected less venous blood through the foramen ovale.

The signs usually associated with tricuspid insufficiency, such as positive venous pulsation in the neck and pulsating liver, occur usually only when heart failure is precipitated by some serious infection, probably mainly because of the great enlargement of the right auricular portion of the heart, which acts as a reservoir, and partly in most cases because of the patency of the foramen ovale. The musculature of the auricular portion of the right ventricle is frequently practically absent, so that this portion of the ventricle plays little part in propelling blood up toward the true auricle.

The condition is compatible with long life, and death from heart failure alone is not the rule. Three patients died unexpectedly. The occurrence of pulmonary tuberculosis in four of the cases is interesting, showing perhaps an increased susceptibility of the lungs because of their reduced blood supply, as in cases of pulmonary stenosis.

Retarded development in the early years of life was noted in several cases, but usually after puberty growth was speeded up. In one case menstruation did not occur, and the uterus was found to be hypoplastic.

OTHER EXAMPLES OF CONGENITAL TRICUSPID INSUFFICIENCY

Ebstein's disease is not the only cause of congenital tricuspid insufficiency. As other interesting examples we should like to refer to the cases of Hotz and of Ariel. Hotz¹⁴ reported two very similar cases, one a girl who died at the age of 13 years, the other a boy who died at 12. In both cases there was cyanosis. In both the heart was enlarged, with accentuation of the pulmonic second sound, and roentgenograms showed marked enlargement in the region of the pulmonary conus. In one there was a variable soft systolic murmur, in the other there was no murmur, but toward the end paralysis of the left recurrent laryngeal nerve and diminution of the left radial pulse developed due to pressure upon the nerve and the aortic arch by the greatly enlarged pulmonary artery and right auricle. Death was due to heart failure with tricuspid insufficiency in both cases. Necropsy revealed that the tricuspid valve had only two short leaflets in one and one well developed and two rudimentary leaflets in the other.

In Ariel's¹⁵ case a cyanotic male infant died after two days. There were lobar pneumonia and passive congestion of all of the organs. Both the mitral and tricuspid valves were represented by tumor-like processes which were interpreted as congenital overgrowths or hyperplasia of the embryonic connective tissue of the endocardial cushions. Microscopic sections showed these anomalous valves to consist of avascular, thick collagen fibers.

SUMMARY

Ebstein's disease of the heart is a rare congenital malformation consisting essentially of downward displacement of the tricuspid valve in an otherwise completely developed heart. The right auricle is greatly enlarged, and the foramen ovale is usually patent. The true right auriculoventricular ostium is enlarged. The tricuspid valve is obviously incompetent, but venous congestion and pulsation do not occur unless an additional strain or damage precipitates heart failure. The condition is not incompatible with long life. Pulmonary tuberculosis is a common complication, probably because of reduced pulmonary blood flow. The lesion may be suspected with other possibilities but can not be positively diagnosed during life.

The sixteenth case is reported. The patient was a woman aged 21 years who was known to have a congenital heart lesion and who died unexpectedly. Necropsy revealed only the heart lesion and acute congestion of the viscera. The electrocardiogram had revealed left axis deviation and prolonged intra-ventricular conduction time. Histologic study of the conduction system by means of 4500 serial sections did not reveal any significant lesion, although the course of the right bundle branch was somewhat anomalous.

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EDITORIAL

THE INCIDENCE OF TRICHINOSIS

Hall and Collins^{1, 2, 3} have recently reported a study of 300 human diaphragms from autopsy cases in 10 hospitals in Washington, D C , and from one hospital in Baltimore which showed that trichinae were present in 13.67 per cent. This figure seems surprisingly high but as Hall points out this is only because we look upon human trichinosis as a rare disease. Previous investigators in different parts of the country have all agreed that latent trichinosis as evidenced by infestation of the diaphragm with trichinae is to be found in a significant percentage of the population. A tabulation of earlier investigations shows percentage incidences found in different sections of the country ranging from 3.5 per cent in New Orleans to 27.6 per cent in Boston. In general the highest incidences were found on the east and west coasts and the lowest in the far south.

This geographic variation the authors are inclined to attribute chiefly to garbage and swill feeding of pigs near the large eastern and western population centers whereas in the south it is more usual for swine to run free in the woods and forage for themselves. In swill and garbage pork scraps are found and such scraps containing trichinae perpetuate the disease in swine. The eating by hogs of trichinae infested rats is a less frequent cause. Both Hall and Schwartz in separate studies showed that live trichinae are far more frequently found in garbage-fed than in grain-fed hogs. The incidence in garbage-fed hogs was 4.8 to 5 per cent and in grain-fed hogs 1 to 1.5 per cent. It is of interest to note that trichinae are to be found far more frequently in the human than in the porcine inhabitants of the United States.

The above data as to geographic variations of incidence in man are not to be accepted as conclusive. The number of cases studied and the methods employed in their study have been too variable to warrant entire confidence in any statistical interpretations. Hall and his coworkers believe, however, that few errors are made in the interpretation of the finding of encysted living or dead trichinae since these are easily recognized, but they feel that unless two or more methods are used many positive cases will be overlooked. In their studies they made a direct microscopic examination of one gram of diaphragm muscle pressed flat between heavy glass plates. In addition varying amounts, averaging 113 grams, of diaphragm were digested in artificial gastric juice for approximately 24 hours and the re-

¹ HALL, M. C., and COLLINS, B. J. Studies on trichinosis. I. The incidence of trichinosis as indicated by postmortem examination of 300 diaphragms, Public Health Reports, 1937, *lii*, 468-490.

² HALL, M. C. Studies on trichinosis. III. The complex clinical picture of trichinosis and the diagnosis of the disease, Public Health Reports, 1937, *lii*, 539-551.

³ HALL, M. C. Studies on trichinosis. IV. The rôle of the garbage fed hog in the production of human trichinosis, Public Health Reports, 1937, *lii*, 873-886.

sultant mixture poured on the screen of a Baermann apparatus. The water coming through as well as the material on the screen were examined for trichinae. The microscopic press-preparation was found most valuable for detecting encysted dead larvae while live larvae were more readily discovered by the digestion-Baermann method. The authors believe that only through semi-quantitative methods applied to very large series of cases in different localities can we obtain a more accurate picture of the prevalence of this potentially serious condition.

In the various reports on the incidence of trichinosis in the United States as determined by postmortem studies of the diaphragmatic muscle Hall found 222 positive cases reported. He was unable to find evidence that a diagnosis of trichinosis had been made in life in a single one of these 222 cases. One reason for this lack of recognition of the infestation may be that in a majority of the cases the number of larvae which entered the circulation and eventually became encysted in the muscles was too small to have caused definite clinical symptoms. It is not known of course whether the number of larvae per gram of diaphragmatic muscle is a dependable index of the concentration of larvae in other portions of the body. We do know that the diaphragm is uniformly attacked and usually contains a high concentration of trichinae. Hall's and Collins' careful work gives the number of trichinae per gram in each of their 41 positive cases. This number is found in their tabulation to vary between 0.006 and 993. In only two cases were there more than 100 trichinae per gram and in only 11 cases were there more than 10 per gram. In 14 cases the average number was less than 1 per gram. No information is yet available to indicate what degree of infestation is necessary to produce the clinical picture of trichinosis but it is probable, Hall and Collins feel, that cases with less than 1 trichina per gram of muscle present few symptoms, and that those with over 100 trichinae per gram show a clear cut clinical picture of trichinosis. Between these extremes there must occur many cases with mild or atypical symptoms which we do not at present associate with clinical trichinosis. There is here undoubtedly an unexplored clinical field. In addition to the symptoms now usually considered as cardinal—gastrointestinal disturbances, fever, sub-orbital edema, painful muscles, pneumonia—we must learn to suspect of trichinosis infestation cases showing certain ocular lesions, atypical myocardial involvement, meningismus, encephalitis with stupor, diaphragmatic pleurisy, urticaria, etc. The search for eosinophilia, the biopsy of muscle, the search for trichina larvae in the blood and cerebrospinal fluid, the skin test and the precipitin test should be applied more freely in our clinical investigations of obscure disease processes.

REVIEWS

The Practitioner's Library of Medicine and Surgery Supervising Editor, GEORGE BLUMER, M A (Yale), M D, F A C P, David P Smith Clinical Professor of Medicine, Yale University School of Medicine, Consulting Physician to the New Haven Hospital *Volume XII Preventive Medicine and Hygiene* Associate Editor IRA V HISCOCK, M A, C P H, Professor of Public Health, Yale University School of Medicine xxxviii + 993 pages, 45 illustrations D Appleton-Century Company, Inc, New York 1937 Price, \$10 a volume

The previous eleven volumes of *The Practitioner's Library* have been reviewed in the ANNALS as they have appeared. The twelfth volume, *Preventive Medicine and Hygiene*, is an interesting and valuable addition to the set. Twenty-five authors, each chosen for special knowledge of some particular field, have contributed the forty-two chapters. The associate editor, Ira V Hiscock, has himself provided nine chapters. The subject matter is grouped into four parts of which Part I deals with Individual Hygiene. Of special interest to the general practitioner are the chapters in this section on General Considerations Concerning the Periodic Health Examination by Haven Emerson and on The Content and Technics of Periodic Health Examinations by Harold S Diehl. The benefits of an annual or semi-annual health audit so overwhelmingly outweigh the arguments against this procedure that the practitioner must be prepared to meet an increasing demand for this form of service. Unless the periodic examination is conducted in a thoroughly scientific manner and its results properly recorded by some such method as described in these chapters, its value may be lost and the procedure fall into disrepute. The practitioner will find these chapters full of practical suggestions applicable to his routine examinations of sick people as well as of those who are presumptively in a state of health. The chapter on Sex Hygiene by M J Eaner and W F Snow is especially valuable. In it the practitioner will find safe and reasoned answers for the many questions which are asked him about juvenile sexuality, masturbation, continence and sex-adjustment in marriage. Part II is devoted to Group Hygiene and will prove of special use to the physician who is the health advisor to a rural community. The hygiene of the home and of educational institutions and the health hazards of farming are topics which are fully developed. Part III deals with Community Health and here will be found basic information on the protection of food and water supplies and on sewage disposal. In the smaller communities the physician is frequently called upon to advise or even direct in such matters. Likewise the control of communicable diseases in general, and of tuberculosis and the venereal diseases in particular, is discussed here. Part IV covers The Prevention of Specific Diseases. The chapter on Prevention of the Infectious Diseases is by William H Park and Morris Seigel, those concerned with Toxic and Physical Agents by Emery R Hayhurst. It is impossible, in a limited review, to refer specifically to each of the chapters treating of prevention of disease in various anatomical systems. As the reviewer has had occasion to write in regard to preceding volumes, this series is remarkably free from typographical errors for a first edition. There is an unavoidable variance in literary style and an occasional lapse into medical slang which is out of harmony with the dignity of the work as a whole. Should we be alarmed or relieved that (p 853) "The mortality in the best clinics is from 2 to 8 per cent of all prostates who enter," or that (p 855) "The future of the testicular tumors is always in doubt"? The nice press work and adequate indexing which have been found in previous volumes are maintained here. This twelfth volume is a worthy addition to the *Library*, and fully qualified to stand alone as an adequate textbook of Preventive Medicine and Hygiene.

C V W

Orthodiascopy By CHESTER M. KURIZ, M.D., F.A.C.P., Assistant Professor of Medicine, University of Wisconsin, Cardiologist to the State of Wisconsin General Hospital. 247 pages, 15 × 22 cm, indexed. The Macmillan Company, New York. 1937. Price, \$3.50.

The author describes the technic of recording orthodiagrams and the apparatus necessary. The normal cardiac silhouette is depicted and in subsequent chapters alterations from normal in size and silhouette due to the various diseases of the heart are discussed. The author's observations indicate that the method of determining the frontal area of the heart described by Hodges and Eyster gives the most reliable evidence of cardiac enlargement and nomograms for determining the expected (normal) frontal area are presented. The author holds that the combination of fluoroscopy and orthodiascopy is the most valuable roentgenologic method of examining the heart and recording its size and contour. With this point of view the reviewer is in entire accord. However, no roentgenologic method as yet devised gives infallible evidence as to whether lesser deviations from an expected normal mean cardiac enlargement. Such decisions ultimately must be based not on measurements alone but on other considerations as well. It is only fair to state that the author recognizes this fact in spite of his enthusiasm for the methods described. It would have been wise to have stressed it more. For many reasons it would seem obvious that the cardiologist is the logical person to perform such examinations. This book is recommended to those interested in this subject.

W. S. L., JR.

Biological Time By P. LECOMTE DU NOUY, Chief of the Division of Molecular Physics, Pasteur Institute, Paris, formerly Associate Member of the Rockefeller Institute. Foreword by Alex. Carrell, M.D. ix + 180 pages, 20 × 12.5 cm. Macmillan Co. New York. 1937. Price, \$2.00.

This interesting volume is divided into three main headings. The first, entitled "The Biological Problem and Methods," compares the methods of the physical scientist with those of the biologist and in it the limitations of physical methods in biology are emphasized.

The second division of the book is entitled, "Cicatrization of Wounds and Tissue Culture." In this a comprehensive survey of the cicatrization of wounds on individuals of various age groups is reported. Many of the observations of the author were made on soldiers during the World War. The rapidity of healing in the young and the delayed cicatrization in late life are clearly demonstrated. Many diagrams are included illustrating these phenomena. Further work in this section is reported on the speed of cicatrization with respect to the area of the wound. Several curves expressing this relationship in various wounds are given and a general exponential equation giving mathematical expression to the subject has been developed.

Part three is entitled, "Time." Much space is given to a consideration of the idiology of time as one of the spacial dimensions. Man's concept of time was plotted against his age and interestingly enough the hyperbolic curves obtained by the plotting of man's concept of the time against age and wound cicatrization against age coincide. Finally the author questions whether quantitative symbols will ever express life or psychological phenomena in general—for mathematics cannot express the beauty life so often embodies.

This book should capture the imagination of the scientifically minded physician.

J. C. K., JR.

The Postmortem Examination By SIDNEY FARBER, M D, Associate in Pathology, Harvard Medical School 201 pages, 16 X 23.5 cm Charles C Thomas, Springfield, Ill 1937 Price, \$3.50

Beginning with a brief historical introduction which sketches the influence of the necropsy upon clinical medicine, this manual proceeds with a detailed consideration of the methods employed in the systematic postmortem examination. The clinical methods of Virchow and Rokitsky are used as the basis of the discussion with alternative procedures mentioned when indicated. The exposition is detailed and clear. Helpful illustrations are included from time to time. A brief reference to the problems presented by the medico-legal postmortem is given, but the reader is referred to other sources for more complete information. Because of the author's experience, the section devoted to necropsies on infants and children is of especial interest. Included also are helpful tables of average weights of organs in both adults and children. An adequate index is presented. The book can be heartily recommended as a useful guide for the neophyte and one which points the way toward a high standard of excellence in the performance of the postmortem examination.

M S S

William Withering The Introduction of Digitalis into Medical Practice By LOUIS H RODDIS, M D, Commander, Medical Corps, U S N 131 pages, 14 X 19.5 cm Paul B Hoeber, Inc New York 1936 Price, \$1.50

The reviewer has not previously read a biography of William Withering, and indeed no other seems to be extant. The author's source material is revealed in the appendix and includes the memoir by Withering's son. One does not gain a very adequate impression of the personality of the man from this biography, but this is doubtless due to the lack of material from which to draw such a picture rather than to any fault of the author. We do see Withering to be a man interested in many scientific pursuits as so many were in his time. We find him to be a botanist of note, a mineralogist, a student of climatological phenomena and an observing clinician. He was interested in the social movements of his day and was a sympathizer with the French Revolution. His medical fame has a secure base in his observations on digitalis. This drug was first brought to his attention in 1775 as a "family recipe for the cure of dropsy." With his botanical knowledge it was not difficult for him to discover that the foxglove was the active ingredient. The author quotes frequently from Withering's writings and includes in the text the section of the book on digitalis dealing with Preparation of the Drug, Effects, Rules and Cautions, Constitution of the Patients, Inferences. Although Withering attributed the therapeutic qualities of foxglove to a diuretic action, but little has since been added to his clinical observations.

W S L, Jr

Weight Reduction, Diet, and Dishes By E E CLAXTON, M B, B S (London), D T M and H 199 pages, 14 X 22 cm William Heinemann (Medical Books) Ltd, 99 Great Russell St, London, W C I 1937 Price, 8s 6d net

This is a readable and useful book on the treatment of overweight, couched in language midway between vernacular and textbook. Endowed with British whimsy, and aimed for the use of the lay person, it proceeds with moderate pedagogical repetition at a slow and steady pace. There is an unusual plowing up of superstitions and a most serious discussion of the disadvantages of being fat. The "banana and milk" diet is properly expounded. An undue emphasis is put on salt and on the ductless glands which are dragged in as a sort of *deus ex machina* whenever the discussion seems to be getting out of hand. The recipes are abundant and explicit. They are unusual in that they make individual servings. It will be a useful handbook for cooperative patients, and an acceptable textbook for dieticians and students.

C A

COLLEGE NEWS NOTES

New Life Member Dr Louise Tayler-Jones (Fellow), McLean, Va., became a Life Member of the American College of Physicians on November 11, 1937

GIFTS TO THE COLLEGE LIBRARY

Receipt is gratefully acknowledged of the following donations to the College Library of publications by members

Books

- Rear Admiral C S Butler (MC), U S N (Fellow), Washington, D C—an autographed copy, "Syphilis Sive Morbus Humanus",
Dr William Fitch Cheney (Fellow), San Francisco, Calif—"The Diagnosis and Treatment of Diseases of the Stomach and Intestines",
Dr J C Geiger (Fellow), San Francisco, Calif—"Bacteriology of Specific Communicable Diseases Handbook of Public Health Bacteriology",
Dr Frank H Krusen (Associate), Rochester, Minn—an autographed copy, "Physical Therapy in Arthritis",
Dr Aaron E Parsonnet (Fellow), Newark, N J, and Dr Albert S Hyman (Fellow), New York, N Y—"Applied Electrocardiography",
Dr Bernard L Wyatt (Fellow), Tucson, Ariz—an autographed copy, "Chronic Arthritis and Fibrositis"

Reprints

- Dr Marcos Fernan-Nunez (Associate), Milwaukee, Wis—"Medicine as a Career",
Dr Fred M F Meixner (Fellow), Peoria, Ill—"Treatment of Pneumonia",
Dr Lewis J Moorman (Fellow), Oklahoma City, Okla—"Francis Adams of Banchory", "Medicine Versus State Medicine", "Multiple Calcifications in the Spleen", "The Home Versus the Preventorium in the Management of Tuberculosis Contacts", "The Tuberculosis Problem"

Acknowledgment is also made of the receipt of a report prepared by the Bureau of Medical Economics of the American Medical Association, entitled "Group Hospitalization"

Dr Currier McEwen (Fellow), New York, N Y, has been appointed Dean of the New York University College of Medicine Dr McEwen is thirty-five years of age, the youngest medical college dean in the United States He graduated from New York University College of Medicine in 1926, and heretofore has been Assistant Professor of Medicine and Assistant Dean and Secretary of his Alma Mater

Dr David I Abramson (Associate), formerly of Brooklyn, N Y, has been appointed Director of Cardiovascular Research in the Institute for Medical Research of the Jewish Hospital, Cincinnati, Ohio, as of November 1, 1937

Dr S A Slater (Fellow), head of the Southwestern Minnesota sanatorium at Worthington, was elected president of the Minnesota Public Health association at the

annual meeting of that organization in St Paul He will assume office January 1, 1938

Dr August A Weiner (Fellow), St Louis, Mo, gave two lectures under the auspices of the Iowa State Medical Society for their postgraduate course at Sheldon, Iowa, on November 1, and at Waterloo, Iowa, on November 2, his subject being "Gonad Hormones in Health and Disease"

The Tenth Annual Graduate Fortnight of the New York Academy of Medicine was held from November 1 to 12, 1937, and was devoted to "Medical and Surgical Disorders of the Urinary Tract" Dr James Alex Miller (Fellow and ex-President), is President of the Academy On the Graduate Fortnight Committee appeared the names of the following Fellows of the College Dr Bernard Sutro Oppenheimer, Chairman, Dr Ralph Henderson Boots, Dr Thomas T Mackie, and Dr Herman O Mosenthal

Among presentations on the program were Dr James Alex Miller (Fellow), Address of Welcome, Dr George Baehr (Fellow), "The Pathology of Nephritis", Dr Robert F Loeb (Fellow), "Clinical Aspects of Nephritis", Dr Herman O Mosenthal (Fellow), "Clinical Aspects of Hypertension, Including Malignant Hypertension", Dr W W Herrick (Fellow), "Vascular and Renal Complications of Pregnancy"

The program of afternoon hospital clinics included presentations by the following Fellows Dr Soma Weiss (Boston), Dr I W Held, Dr William Goldring, Dr Walter W Palmer, Dr Robert F Loeb, Dr George A Sheehan, Dr B P Stivelman, Dr B S Oppenheimer, Dr A M Master, Dr Herman O Mosenthal, Dr Benjamin I Ashe, Dr Lewis A Conner, Dr C E de la Chapelle, Dr W W Herrick, Dr S Edward King, Dr Albert S Hyman, Dr Maximilian A Ramirez, Dr James R Lisa and Dr I Seth Hirsch

At the annual meeting of the California Section of the American Sanatorium Association, held at Orange, California, November 12, 1937, the following Fellows participated, Dr E W Hayes (Fellow), acting as one of the hosts Dr H G Trimble, presentation of report on resolutions to the American Sanatorium Association and the National Tuberculosis Association, Dr Chesley Bush, resume of the present status of the Association of Thoracic Surgeons, Dr F M Pottenger, follow-up program of cases discharged with a favorable result from the Tuberculosis Sanatorium, Dr Chesley Bush (with Dr Everett Morris), choosing a site for the new Tuberculosis Sanatorium, urban vs rural locations, a division of the General Hospital or individual entity, Dr Harold G Trimble (with Dr W A Hodges), the present place and future development of the Preventorium

Dr Edward J Engberg (Fellow), St Paul, Minn, has been appointed Superintendent of the School for Feeble-Minded at Faribault, Minn, by the State Board of Control

Dr Byrl R Kirklin (Fellow), Rochester, Minn, Professor of Radiology in the University of Minnesota Graduate School of Medicine (Mayo Foundation), and Dr Harry M Weber received the first award for their exhibit at the International Con-

gress of Radiologists at Chicago during September Dr Kirklin was elected President of the Roentgen-Ray Society

Dr Thomas B Magath (Fellow), Rochester, Minn, Professor of Parasitology in the University of Minnesota Graduate School of Medicine (Mayo Foundation), has been elected President of the American Society of Clinical Pathologists Dr Magath is the City Health Officer in Rochester

Dr Henry L Ulrich (Fellow), Minneapolis, Minn, Professor of Medicine at the University of Minnesota Medical School, has been installed as President of the Hennepin County Medical Society

Dr J Richards Aurelius (Fellow), St Paul, Minn, and Dr Louis E Prickman (Associate), Rochester, Minn, have been elected Secretary and Treasurer, respectively, of the Alumni Association of the Mayo Foundation

Dr Horton Casparis (Fellow), Nashville, Tenn, Professor of Pediatrics, Vanderbilt University Medical School, and Dr Julius H Hess (Fellow), Chicago, Ill, Professor of Pediatrics, University of Illinois Medical School, were guest speakers on the postgraduate symposium on Diseases of Women and Children held at Duke University, Durham, N C, November 11 to 13

Dr Douglas Martin (Fellow), Tampa, Fla, and Dr Warren W Quillian (Fellow), Coral Gables, Fla, have been elected President and Secretary, respectively, of the Florida Pediatric Society

Dr Oliver B Kiel (Fellow), Wichita Falls, Tex, has been elected President of the Texas State Board of Medical Examiners

Dr Edgar M Dunstan (Fellow), Dallas, Tex, has been appointed Superintendent of the Dallas City and County Hospital System

Dr Walter E Vest (Fellow and Governor), Huntington, W Va, has been elected President of the Public Health Council of West Virginia

Dr E H Shuller (Associate), McAlester, Okla, has been elected President of the Southeastern Oklahoma Medical Association

Dr Priscilla White (Fellow), Boston, Mass, was one of the guest speakers at a scientific meeting of the Georgia Pediatric Society at Atlanta, December 9

Dr Samuel A Levine (Fellow), Boston, Mass, Professor of Medicine, Harvard Medical School, and Dr Cyrus C Sturgis (Fellow), Ann Arbor, Mich, Professor of Medicine and Director of the Simpson Memorial Institute for Medical Research, University of Michigan were guest speakers on the program of the Oklahoma City Clinical Society's Conference, November 1 to 4, 1937

The Twelfth Series of Friday Afternoon Lectures sponsored by the New York Academy of Medicine for 1937-38 is made up, in part, by the following November 19, 1937—Dr Robert L Levy (Fellow), New York, N Y—"Drugs in the Treatment of Heart Disease", December 17, 1937—Dr Eugene M Landis (Fellow), Philadelphia, Pa—"Recent Advances in the Diagnosis and Treatment of Peripheral Vascular Diseases", January 7, 1938—Dr Rufus Cole (Fellow), Mount Kisco, N Y—"Treatment of Pneumonia", February 18, 1938—Dr William Thalhimer (Fellow), New York, N Y—"Convalescent Measles and Scarlet Fever Serums Their Value in Prophylaxis and Therapy", March 4, 1938—Dr Milton A Bridges (Fellow), New York, N Y—"The Evaluation of Recent Therapeutic Procedures", March 11 1938—Dr Thomas T Mackie (Fellow), New York, N Y—"Various Types of Colitis, with Particular Reference to Ulcerative Colitis", March 18, 1938—Dr James Ralph Scott (Fellow), New York, N Y—"The Modern Treatment of Diabetes Mellitus"

Dr Edward S Sledge (Fellow) President of the Alabama State Medical Association, addressed the Gulf Coast Clinical Society at Biloxi, Miss, on November 3 on "The Clinical Value and Limitations of Electrocardiography"

Other Fellows who contributed to the program were Colonel Charles F Craig, New Orleans, La, Dr Horton R Casparis, Nashville, Tenn, Dr William C Chaney, Memphis, Tenn, Dr Ray M Balyeat, Oklahoma City, Okla

Dr Lewis M Hurxthal (Fellow), Boston, Mass, was a guest speaker on the program of the Medical Institute of the University of Toledo on November 19, 1937

Dr Walter F Donaldson (Fellow), Pittsburgh, Pa, has been reelected Secretary of the Medical Society of the State of Pennsylvania

Dr Russell L Haden (Fellow), Cleveland, Ohio, and Dr William D Stroud (Fellow and Treasurer), Philadelphia, Pa, were among the guest speakers on the program of the Post-Graduate Medical Assembly of South Texas, at Houston, November 2 to 4

The Annual Congress of the Pan American Medical Association will be held January 15-31, 1938, aboard the S S Queen of Bermuda, on a cruise to Havana, Port au Prince, Trujillo City and San Juan Among chairmen of sections are the following Colonel Charles F Craig (Fellow), New Orleans, La—"Tropical Medicine", Dr Jay A Myers (Fellow), Minneapolis, Minn—"Thoracic Section", Dr Howard R Hartman (Fellow), Rochester, Minn—"General Medicine", Dr Edwin

C Ernst (Fellow), St Louis, Mo—"Radiology", Dr Orville E Barbour (Fellow), Peoria, Ill—"Pediatrics"

Dr Henry A Luce (Fellow), Detroit, Mich, is President-Elect of the Michigan State Medical Association

Dr Charles E Sears (Fellow), Portland, Ore, is President-Elect of the Oregon State Medical Society

Dr Raymond G Taylor (Fellow), Los Angeles, Calif, is President-Elect of the Radiological Society of North America

Dr Carleton B Peirce (Fellow), Ann Arbor, Mich, is Secretary of the American Roentgen-Ray Society

Dr Walter C Swann (Fellow), Huntington, W Va, was elected President of the Cabell County Medical Society for the year, 1938

Research Fellowships Available Fellowships in the medical sciences for the year beginning July 1, 1938, have been announced by the National Research Council. Fellowships are open to citizens of the United States and Canada who have the degree of doctor of medicine or doctor of philosophy. The Fellowships are intended primarily for recent graduates, and not for persons already established professionally. Applications should be filed by January 1, 1938. Appointments will be made at a meeting of the Medical Fellowship Board about March 1, 1938. Additional information may be obtained from the Secretary of the Medical Fellowship Board, National Research Council, 2101 Constitution Avenue, Washington, D C

REGIONAL MEETING OF VIRGINIA MEMBERS

A Regional Meeting of the Fellows and Associates of the American College of Physicians residing in Virginia was held, in connection with a Banquet, at the Shenandoah Club, Roanoke, Va, October 12, 1937, with twenty-six members present.

The Virginia members have organized their group under a local President and Secretary. Dr J W Preston, of Roanoke, was elected President of the local chapter to succeed Dr W B Martin, and Dr George B Lawson, of Roanoke, was elected Secretary to succeed Dr F C Rinker.

There was a general discussion concerning the present method of distributing inquiry cards to all Fellows concerning new candidates. The By-Laws of the College, Article V, Section 2, after covering the method by which a candidate shall be nominated, states "Further, the name of the candidate shall be sent to each Fellow in the candidate's locality, with a request for comments as to the candidate's fitness." This has been accomplished through cards sent out from the Office of the Executive Secretary after the receipt of each proposal.

A resolution was adopted referring to the Board of Regents, through the Executive Secretary, the recommendation that this system be changed, and in its

place a system adopted whereby regional committees shall be appointed, consisting of about four or five members located in different sections of each state, whose duty it shall be to investigate and reply to all letters of inquiries in regard to eligibility of new members

A further resolution was adopted that the Virginia Chapter of the College hold two regional meetings per annum, one at the Medical College of Virginia, in Richmond and the other at the University of Virginia, at Charlottesville

CORRECTIONS, 1937 DIRECTORY

It is regretted that two errors have been made in the names of Fellows of the College in connection with our biographical listing in the 1937 Directory. It is requested that members of the College reading this notice will kindly record these corrections in their directories.

Page 386, JORDAN, Sara Murray (the spelling J-o-r-d-o-n is incorrect)

Page 425, MACCRACKEN, Walter H (the spelling, M-a-c-C-r-a-c-k-e-n is incorrect)

OBITUARIES

DR JOHN L CHESTER

Dr John L Chester (Fellow) of Detroit, Michigan, died May 31, 1937

Dr Chester was born in New York State, but came with his family to Michigan at an early age. He received his medical degree from Saginaw Valley Medical College in 1901, and started practice in Emmet, Michigan. In 1917, he moved to Detroit and practiced there until the time of his death, confining his practice to Internal Medicine. His work was largely in the field of cardiology, on which subject he published a number of papers.

Dr Chester held staff positions at Providence Hospital (Chief-Elect), and at Seymour Hospital, Eloise, in which institution he was Physician in Chief, Division of General Medicine. He was active in teaching, and held appointment as Professor of Clinical Medicine in Wayne University College of Medicine. He was a Fellow of the American College of Physicians since 1926.

Dr Chester was a very earnest student in his field, and his death will be a great loss to his large practice, as well as to the profession. He was active in all local medical society activities, read many papers before medical groups, and took a particularly keen interest in the internes and younger members of the profession, whom he was always ready to help with counsel and advice. The profession has lost an able clinician and a good friend.

HENRY R CARSTENS, M D , F A C P ,
Governor for Michigan

DR ISAAC IVAN LEMANN

Dr Isaac Ivan Lemann (Fellow, 1920) of New Orleans, who was born at Donaldsonville, Louisiana, 1877, and died on September 2, 1937, will be sadly missed not only by the members of the medical profession of New Orleans and the State of Louisiana but by his many friends and admirers throughout the Nation.

Dr Lemann was gentle and modest in his relations with other members of the profession. He was especially considerate and charitable toward the younger members of his profession. He was admired and loved by the student bodies of the institutions with which he was connected. Dr Lemann made many valuable contributions to medical literature, outstanding among these was his work and published papers on diabetes. He was recognized as a clinician of superior ability, and personally a most lovable individual.

Dr Lemann received the A B degree from Tulane University in 1895, A B from Harvard University in 1896, M D from Tulane University of Louisiana School of Medicine in 1900. Instructor in Clinical Medicine, Tulane University of Louisiana School of Medicine, 1906-1910, Assistant

Professor of Clinical Medicine, Tulane University of Louisiana School of Medicine, 1910-1914, Professor of Clinical Medicine, Tulane University of Louisiana School of Medicine, 1914-1937, Chief of Medical Service, Touro Infirmary, New Orleans, Consultant in Medicine, Charity Hospital, New Orleans, Senior Consultant in Medicine, Flint Goodridge Hospital of Dillard University, Vice Chairman of the Section on Practice of Medicine, American Medical Association, 1932-1933, Fellow of the American College of Physicians since 1920, Member Orleans Parish Medical Society, Louisiana State Medical Society, American Medical Association, Southern Medical Association, American Society of Tropical Medicine, Southern Inter-urban Clinical Club, Association of American Physicians, and the American Clinical and Climatological Association

The College has suffered a severe loss in the passing of Dr Lemann and he will be sorely missed as a Member of the faculty of Tulane University and in relation to his hospital connections

J E KNIGHTON, M D , F A C P ,
Governor for Louisiana

DR HARRY GILMER WALCOTT

Dr Harry Gilmer Walcott (Fellow 1928), aged sixty, a native Texan, died June 2 1937, in a Dallas hospital after a long illness

Dr Walcott was a descendant of pioneer Texas stock His academic education was obtained at Austin College in Sherman, Texas, and the Holbrook Normal School in Tennessee In 1901 he graduated with high honors from the Baltimore Medical College, where he remained as Associate Professor of Physiological Chemistry for one year He then returned to his old home at Honey Grove Texas, where he engaged in practice until April 1903, when he went to Chicago for a period of study under an association with the late Dr Fenton B Turck While in Chicago Dr Walcott gave particular attention to the study of disorders of digestion Later in 1903 he moved to Dallas Texas, to enter the practice of gastro-enterology He was the first physician in the state to practice this specialty exclusively, and was throughout the years a recognized leader in his section For a period of years he was professor of gastro-enterology in Baylor Medical School, and at the time of his death was an emeritus professor Perhaps to Dr Walcott more than to any other person belongs the credit for the placing of gastro-enterology on a high plane in Texas

During the World War he served with distinction as a Captain in the Medical Corps of the United States Army

To those who knew him best Dr Walcott exemplified and practiced the highest ethical tenets of the profession He was zealous of the welfare of his patients affectionate and indulgent with his family, a loyal friend and a wise counselor to those who sought his opinion and advice

He is survived by his wife, a son, Harry Gilmer Walcott, Jr., and a daughter, Mrs William Lipscomb

CHARLES T STONE, M D, F A C P,
Governor for Texas

DR ELIJAH LUMBIA MASON

Dr Elijah Lumbia Mason was born February 25, 1871, in Rocky Mount, Virginia, the son of Gilbert and Susan Goode Mason, of Virginia. He was educated in private schools. He was a resident of the District of Columbia since 1894. He was graduated in pharmacy from the National College of Pharmacy, 1896, and was graduated in medicine from Columbian (now George Washington) University, 1901.

Dr Mason was married to Viola V Hines of Virginia in 1906, and they had one child, Jack Wellons Mason. His wife and son survive him.

Dr Mason was a member of the following organizations: Fellow of the American Medical Association, Fellow of the American College of Physicians, Medical Association of the District of Columbia, April 2, 1902, Medical Society of the District of Columbia, October 1, 1902 (Seniority Number 298), the Hippocrates-Galen Society, of which he was a past president, the Phi Sigma Kappa Fraternity. He was consulting physician to the Washington City Orphan Asylum, and to the Episcopal Eye, Ear and Throat Hospital. He was associate in Medicine of the Garfield Memorial Hospital.

He was connected with the Children's Hospital as pharmacist and after graduation in medicine as resident physician and pathologist.

On September 5, 1932, following an accident at Gallinger Municipal Hospital, he was totally incapacitated for practice. He died on August 30, 1937, as the result of bronchopneumonia.

It is difficult to draw any valid conclusions from such meager data, as to the character and life of Dr Mason. But from those who came in contact with him for the more than forty years of his activities in Washington the record can be fully made up. Quiet and courteous in his dealings with others, conscientious and thorough in his professional work, gracious and kindly with his friends, always a gentleman. Such characters are an inspiration to those coming in contact with them, and to those coming after. His passing is a distinct loss to the profession.

V B JACKSON, Chairman,
J D THOMAS and F R HAGNER,
Committee

(Presented before the Medical Society of the District of Columbia, November 10, 1937.)



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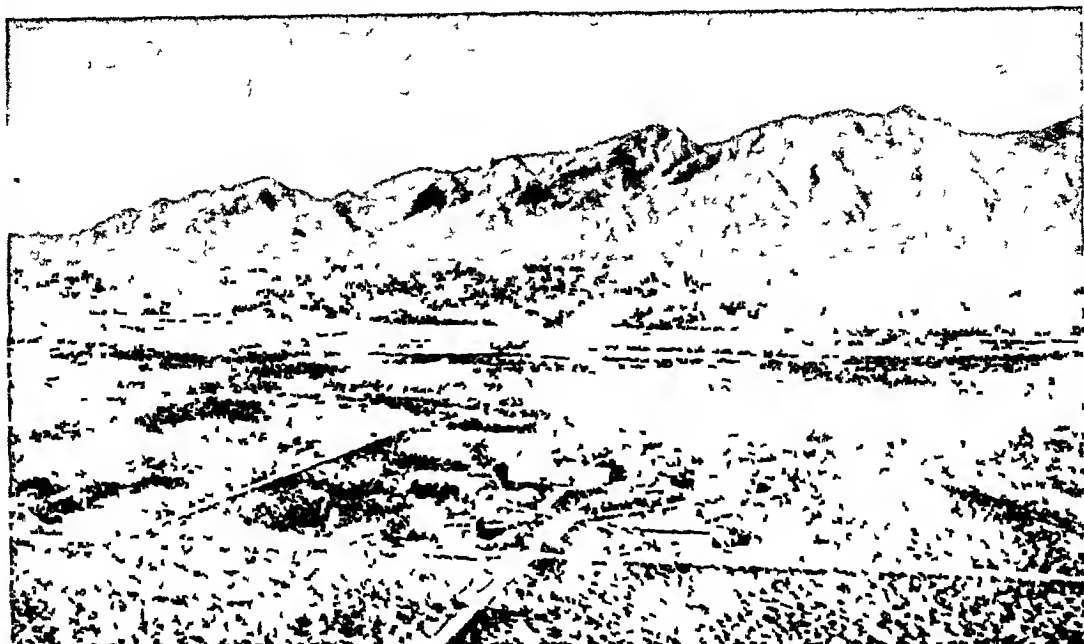


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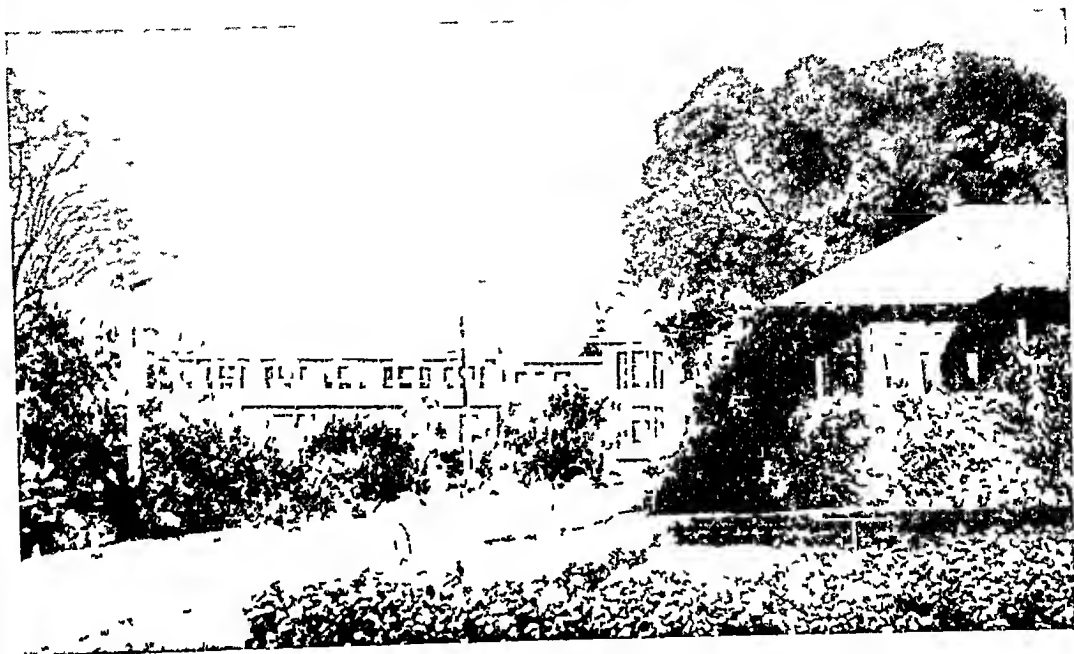
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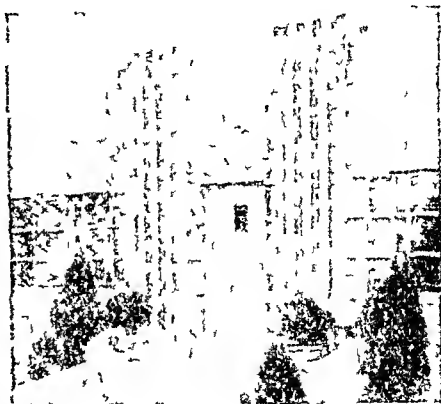
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Place of Publication—Prince and Lemon Sts, Lancaster, Pa

Editorial Office—University Hospital,
Baltimore, Md

Executive Office—4200 Pine Street,
Philadelphia, Pa

THE ANNALS OF INTERNAL MEDICINE is published by the American College of Physicians. The contents consist of contributions in the field of internal medicine, editorials, book reviews, and a section devoted to the affairs of the College.

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ANNALS OF INTERNAL MEDICINE

PUBLISHED BY

The American College of Physicians

VOL 11 (O S, Vol. XVI)

JANUARY, 1938

NUMBER 7

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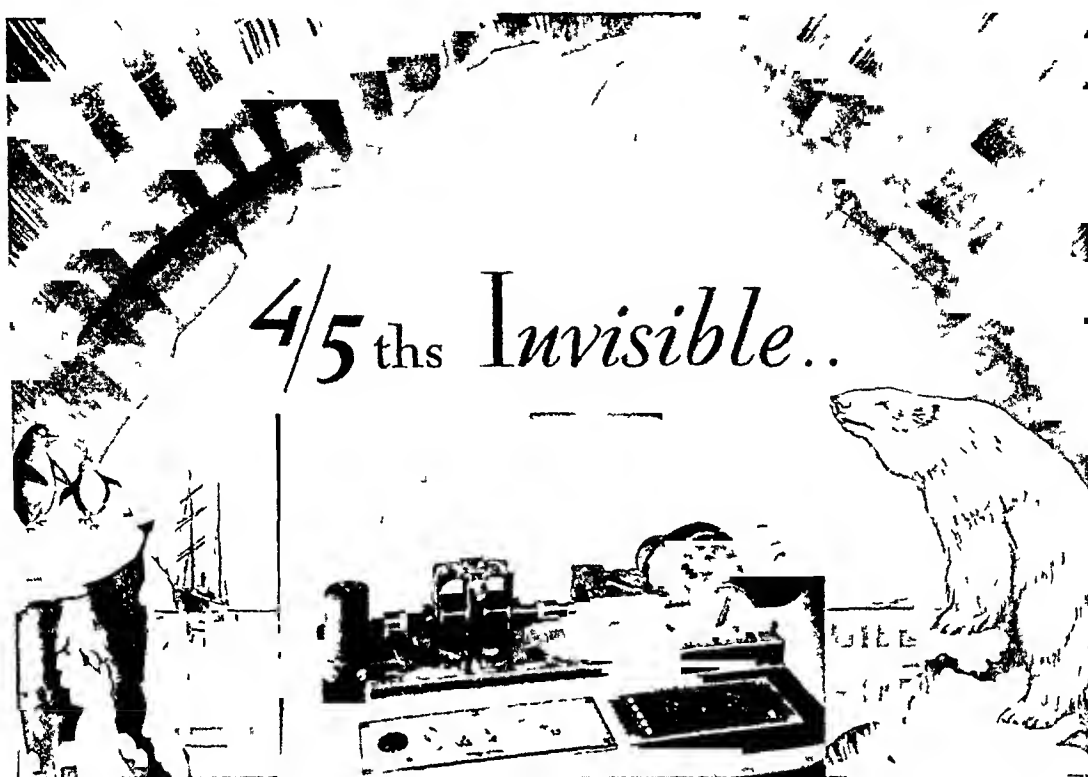
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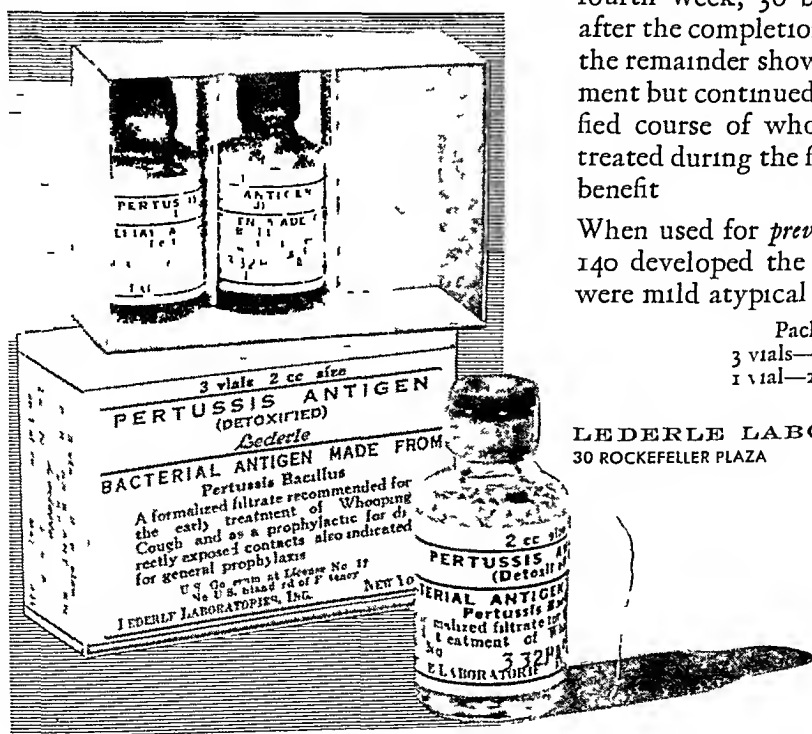
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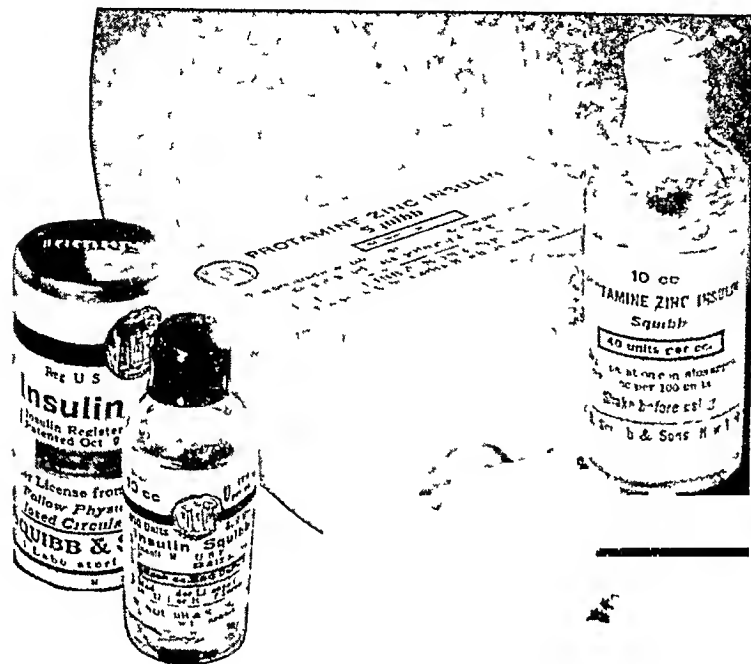
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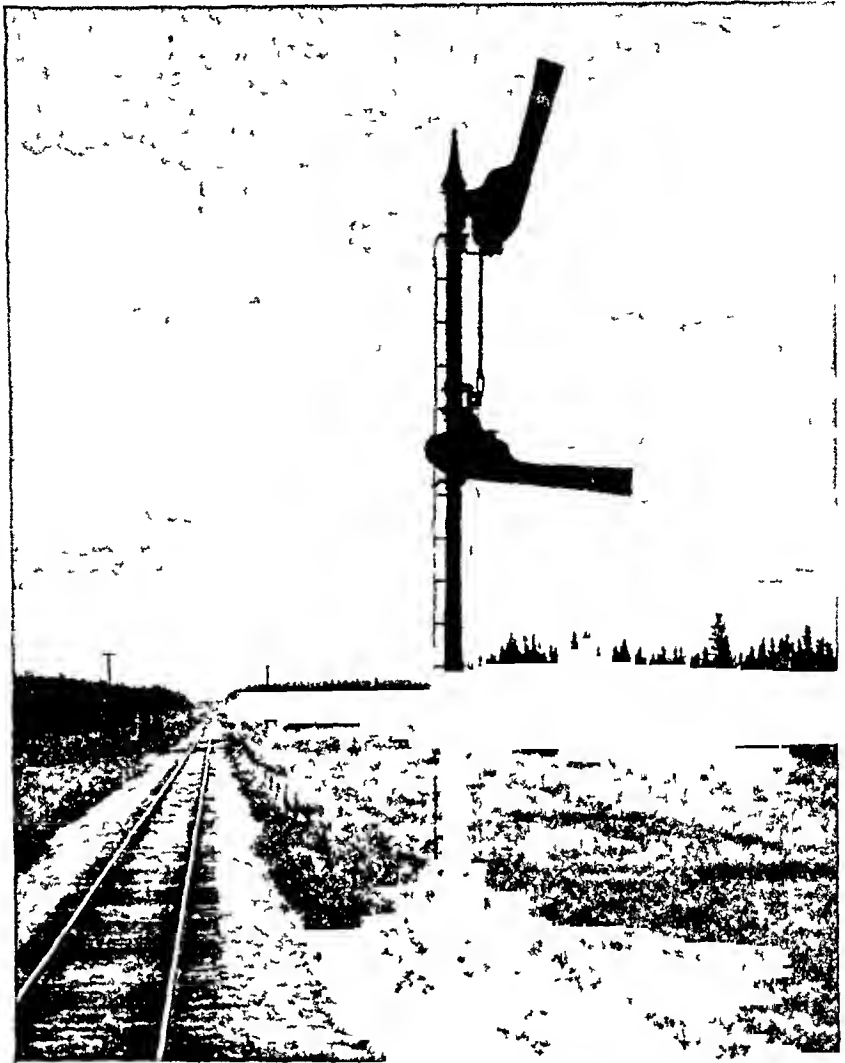
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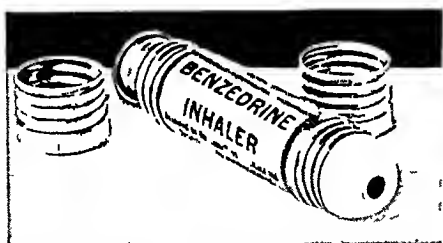
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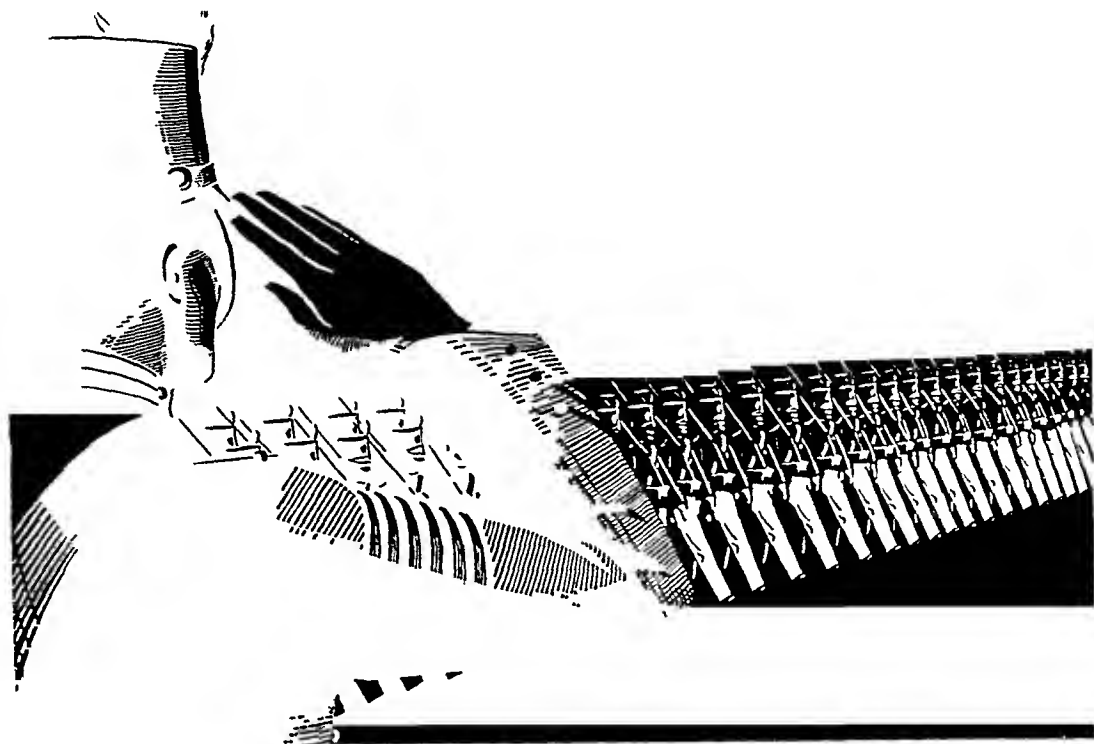


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- 1 Johnson C A A Study of Neo Synephrin Hydrochloride in the Treatment of Acute Shock from Trauma or Hemorrhage, Surg Gynec and Obst 63 35 (July) 1936
- 2 Johnson C A Neo Synephrin Hydrochloride in the Treatment of Anesthesia



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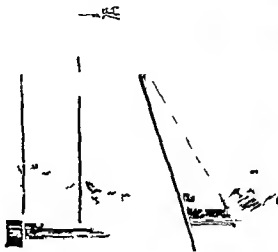
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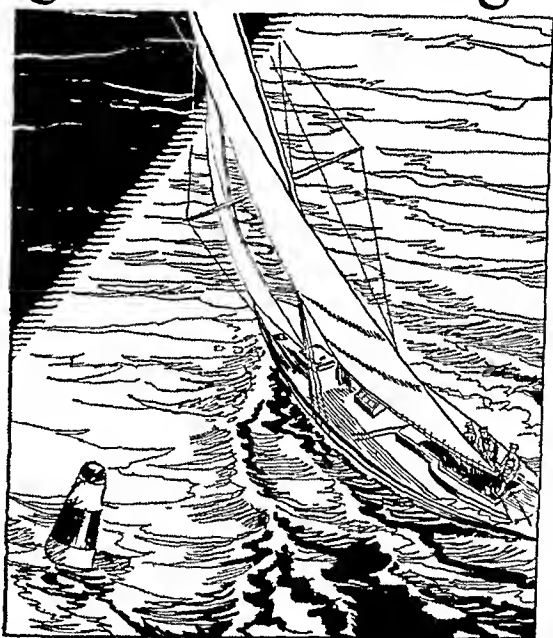
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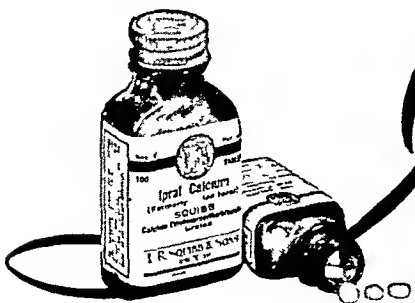
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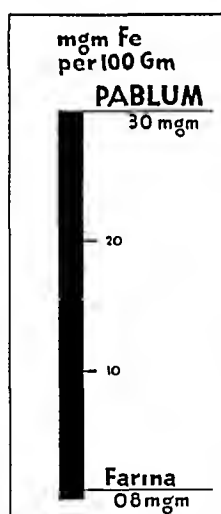
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¹⁻² Bibliography on request

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ANNALS OF INTERNAL MEDICINE

VOLUME 11

JANUARY, 1938

NUMBER 7

THE TREATMENT OF RHEUMATOID ARTHRITIS WITH AN INJECTABLE FORM OF BEE VENOM *

By JACQUES KRONER M D , ROBERT M LINTZ, M D , MARION TYNDALL,
M D , LEONORA ANDERSEN, M D , and EDITH E NICHOLLS, M D ,
New York, N Y

FOR many generations there has been prevalent among the rural population of European countries and to a lesser extent in America, a belief that the sting of bees is a cure for rheumatism Beck,¹ in 1935, published a book on this subject and he traced the use of bee sting and bee venom from antiquity up to the present time Bee-keepers were the first to use bee sting in the treatment of rheumatic conditions and it is only within the past 50 years that physicians have adopted it as a therapeutic measure The first medical report of its use for rheumatoid arthritis was published in 1859 by Demartis² of Bordeaux Terč,³ in Austria in 1880, was the first to use bee sting in his practice as a form of therapy for rheumatoid arthritis and neuritis, and he so treated a large number of patients He published several favorable reports concerning its value but was unable to arouse much enthusiasm among the members of the medical profession During the past 30 years bee sting therapy has been used in European countries with increasing favor

In 1928, Pollack,⁴ in Munich, and Kretschy⁵ in Vienna produced an injectable form of bee venom This product is now made in the chemical laboratories of Dr August Wolff in Bielefeld, Germany, under the name of "Apicosan" The composition and method of preparation of "Apicosan" have not as yet been published, but the authors claim that it "contains the natural secretion of the honey bee in physiological saline solution" Favorable reports of its use for the various forms of rheumatism have been published by physicians in Berlin, Vienna and Geneva

* Received for publication March 10, 1937

From the New York Hospital, and the Department of Medicine of Cornell University Medical College, New York City

The bee venom used in this experiment is a preparation called "Apicosan" manufactured by Dr August Wolff, Bielefeld, Germany, and dispensed in the United States through A W Kretschmar, Inc, New York City

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However, in spite of the many articles that have appeared on the use of bee venom for the treatment of rheumatism there is hardly one that presents evidence of a scientific application of this form of therapy. In most instances, the type of rheumatic disease studied is not clearly defined, the number of patients treated is small, and only generalized statements regarding the results are given.

PRESENT STUDY

The present study was undertaken in order to determine the merits of bee venom in an injectable form (*Apicosan*) in the treatment of rheumatoid arthritis. The patients included in this report were all ambulatory and were treated in the Arthritis Clinic of the New York Hospital. The patients were intelligent and cooperative and were permitted to pursue their usual occupations. An attempt was made to select only patients in whom a focus of infection had been removed some time previously, or in whom none had been found. A few patients were included, however, who had diseased tonsils, the removal of which was contra-indicated. Many of the patients had undergone various forms of therapy without relief.

The patients included in the present study were divided into four groups. One group comprises patients with a markedly active and advanced form of arthritis—deformities such as ulnar deviation and partial or complete ankylosis of one or more joints characterize this group. A second group includes patients presenting the typical picture of well developed rheumatoid arthritis with the characteristic periarticular swelling of the joints, usually including fusiform fingers. A third group comprises those who complained of severe pain in the joints but who failed to show any evidence of arthritis at the time of examination, other than tenderness and stiffness of the joints. In the tables these three groups have been represented by the symbols +++, ++, and +, respectively. All of these patients were found to have an elevated corrected sedimentation index on admission. There is a fourth group, similar to group three except for the fact that the patients had a corrected sedimentation index within the normal range.

Forms of treatment supplementary to the bee venom injections were limited to a minimum. An unrestricted diet, high in vitamins, was usually recommended. Acetyl salicylic acid was frequently prescribed for the relief of pain and patients were advised to apply heat to the affected joints. Cod liver oil was given in many cases.

One hundred patients were studied—25 male and 75 female. The youngest patient was 21 years of age and the oldest 74 years. Thirteen patients were under 30 years of age, fifty-seven ranged in age from 30 years to 50 years and thirty were over 50 years of age.

The duration of the arthritic symptoms ranged from three weeks to 60 years. Thirty-six patients had had arthritis for one year or less, 38 patients between two and five years, and 26 patients more than five years.

Because of the tendency of patients with rheumatoid arthritis, who have been relieved of their symptoms, to suffer relapses or to develop transitory pains in the joints, we have not classified any of our cases as *cured*, being content to use the word *improved*. Improvement was judged by a fall in the corrected sedimentation index, if previously elevated, and an alleviation of the clinical symptoms. Care was exercised not to confuse temporary changes due to climatic or other varying conditions with more lasting ones. No patient has been included who has not been under observation for at least two months and many have been followed for a year or more.

METHOD

All injections were given intradermally. The site selected depended upon the location of the most painful joints. The skin was cleaned with alcohol and wiped dry with benzene. *Apicosan* comes in four different concentrations, N, I, II and III. Strength N is a 1:10,000 dilution of concentration I. One c.c. of concentration I is said to contain the venom of one bee sting, 1 c.c. of concentration II, of three bee stings, and 1 c.c. of strength III, of nine bee stings.

The initial or test dose was 0.1 c.c. of concentration N, injected slowly intradermally forming a wheal. If no reaction followed this injection then 0.1 c.c. of concentration I was given, at the next visit. The treatments were continued at weekly or biweekly intervals, increasing 0.1 c.c. at each visit. Only 0.1 c.c. was put into a wheal and the wheals were placed about one inch apart. When a patient had received 0.5 c.c. of concentration I, or 5 wheals, he was given 0.1 c.c. of concentration II which was increased to 0.5 c.c. and then concentration III was started. The dose was then increased 0.1 c.c. at each visit until the patient was receiving one ampoule of concentration III. All injections were watched for five minutes. If large pseudopodia developed in the wheals, they denoted sensitivity and the dose was not increased for several visits. With one exception, only those patients were included in the study who had received six or more injections.

The sedimentation test used in this study was that recommended by Rourke and Ernstene,⁶ and the figure indicating the sedimentation rate is known as the *corrected sedimentation index*. An index of 0.4 or less was considered normal.

RESULTS

One hundred patients with rheumatoid arthritis were treated with intradermal injections of bee venom (*Apicosan*) and 73 showed definite improvement, as judged by a fall in the corrected sedimentation index and an alleviation of the clinical symptoms (table 1). Seventeen of these were found to be entirely free of symptoms six months to a year after the treatments were discontinued, 18 continued to have mild transitory pains only and 38 were moderately improved.

TABLE I

Results of Treatment with Bee Venom (*Apicosan*) of 100 Patients with Rheumatoid Arthritis

Severity of Disease	Number of Patients	Markedly Improved		Moderately Improved		Total Improved		Unimproved	
		Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
+++	10	0	0	6	60	6	60	4	40
++	36	12	33	15	41	27	75	9	25
+	24	13	54	7	29	20	83	4	17
+*	30	10	33	10	33	10	66	10	33
Total	100		35		37		73		27

* = Patients having a corrected sedimentation index within the normal range

Ten of the patients studied had an advanced, active deforming type of arthritis and six of these showed moderate improvement. Thirty-six patients had severe pain and swelling of the joints and of these 12 showed marked improvement, 15, moderate improvement, while nine failed to respond to treatment. Twenty-four patients were treated who had severe pain and stiffness of the joints but no evidence of swelling at the time of examination and all but four showed improvement, 13 improving markedly, and seven moderately. Thirty patients had joint pains and stiffness similar to the above group but a corrected sedimentation rate within the normal range at the time of admission. Ten of these patients showed marked improvement, 10 moderate improvement, and 10 no improvement.

A patient was not considered improved unless there was a drop in the corrected sedimentation index, if previously elevated, as well as improvement in the clinical symptoms. In table 2 is shown the average corrected sedimentation index for the +++, ++, and + groups, before and after treatment, of the patients who improved as compared with those who failed to respond.

TABLE II

Effect of Treatment on the Corrected Sedimentation Index

Severity	Average Corrected Sedimentation Index			
	Patients Improved		Patients Unimproved	
	Before Treatment	After Treatment	Before Treatment	After Treatment
+++	1.43	0.92	1.28	1.38
++	1.18	0.71	0.90	1.03
+	0.73	0.45	0.91	*

* = Two of the four patients in this group failed to return for a repeat test

As might be expected, the average corrected sedimentation index was higher for the patients with more advanced arthritis. There were 10 in this group and the corrected sedimentation index before treatment ranged from 0.7 to 2.0, with seven having an index of 1.4 or higher. The corrected sedimentation rate for the patients with a moderately severe arthritis ranged from 0.5 to 1.6, with 80 per cent having an index of 1.0 or higher. For the patients showing a mild form of arthritis the corrected sedimentation index ranged from 0.4 to 1.4 with 75 per cent having an index of 1.0 or less. Following treatment there was a drop of five points in the average corrected sedimentation index for the patients showing improvement in the +++ and ++ groups and a drop of three points for the patients in the + group.

It was a matter of interest to compare the number of injections and duration of treatment of the patients who improved with those who did not. In treating ambulatory patients in a clinic it is difficult to control the number of visits. Many patients become discouraged and fail to return after a few visits. In table 3 is shown the average number of injections and average duration of treatment for the three groups of patients studied.

TABLE III

Relationship of Number of Injections and Duration of Treatment to Improvement

Severity	Average Number of Injections		Average Duration of Treatments	
	Improved	Unimproved	Improved	Unimproved
			(Months)	
+++	31.5	18.5	5.6	2.6
++	21.5	15.5	4.5	2.5
+	18.7	13.7	3.8	1.9
+*	14.5	15.9	3.2	3.5

* = Patients having a corrected sedimentation index within the normal range

Of the 10 patients with advanced arthritis the number of injections for the six who improved was 8, 17, 27, 37, 48, and 52 respectively, with an average of 31.5, while the four who failed to improve had 9, 13, 24, and 28 injections, with an average of 18.5. The duration of treatment for the former varied from two to 14 months and for the latter, from two to four months.

For the patients with a moderately severe arthritis the range of injections was from nine to 48 with an average of 21.5 for those who improved, while it varied from six to 25 with an average of 15.5 for those who did not respond. In the improved group half of the patients received 20 or more injections, while only two of the nine patients in the unimproved group

received as many. The duration of treatment for the former varied from one to 12 months, while for the latter it varied from one to four months.

For the patients with a mild arthritis and an elevated corrected sedimentation rate the number of injections for those who improved varied from six to 38 with an average of 18.7 and the duration of treatment from one to 10 months, while for those who failed to respond it ranged from eight to 26 injections with an average of 13.7 and a duration of from one and a half to three months. For the patients with a mild arthritis and a normal corrected sedimentation rate the average number of injections was 14.5 with an average duration of 3.2 months for the improved group and 15.9 injections over a period of 3.5 months for the unimproved group.

Very few untoward reactions occurred from the injections. One patient who was given a much larger dose than on the previous visit developed a severe urticaria immediately after the injection. It cleared up rapidly following an injection of adrenalin. One patient was given three wheals in the left forearm at the third visit. Two of the wheals disappeared in a few hours but one became inflamed and a cellulitis developed in the left hand and wrist two days later which required hospitalization and surgical intervention. Cultures from the site of injection were negative. The patient was found to have a history of recurring attacks of hay fever. Following the reaction the patient had complete relief from the arthritic condition and was well one year later.

DISCUSSION

The highest percentage of improvement occurred in the group of patients having a mild form of arthritis but with an elevated corrected sedimentation rate. However, the patients with the same form of arthritis but having a normal corrected sedimentation index did not respond well to treatment. This is probably due to the fact that many of the latter group were old or quiescent cases and some may not have had a true rheumatoid arthritis. This type of patient does not respond well to any of the usual forms of therapy.

As might be expected, improvement was directly related to the duration of treatment. The patients who improved had injections on an average of two to three months longer than those who failed to respond. Like most forms of therapy for rheumatoid arthritis it was necessary to continue the injections over a long period of time to get the best results.

In giving bee venom in the form of *Apicosan* care must be exercised in order to avoid reactions. The dose should be increased slowly and the patient should be questioned at the next visit regarding redness, pain and swelling at the site of the injection. The test dose (0.1 c.c. of concentration N) should always be given preliminary to starting the treatments as some people are very sensitive to bee venom.

It is of interest to compare the results obtained in this study with those following the use of vaccine. In 1933 Stainsby and Nicholls⁷ reported an improvement of 58.3 per cent in a group of 103 patients treated by the removal of diseased tonsils and injections of hemolytic streptococcus vaccine. One hundred and ninety-four patients in whom the focus of infection had been removed before coming to the clinic were treated with vaccine only and 35.9 per cent showed improvement.

SUMMARY

1 One hundred patients with rheumatoid arthritis were treated with an injectable form of bee venom (*Apicosan*) and 73 showed improvement. Thirty-five of the patients were markedly improved and 38 moderately improved. There was definite and lasting relief from the pain and swelling and a drop toward normal in the corrected sedimentation rate, if previously elevated.

2 The number of injections varied from 6 to 52 over a period of from one to 14 months. The patients who received on the average a longer course of treatment showed the greater improvement.

3 In estimating the results obtained from this study of an injectable form of bee venom (*Apicosan*) for rheumatoid arthritis one is impressed with the definite improvement in the clinical symptoms and the significant drop in the corrected sedimentation index in a large percentage of the patients. It would seem, therefore, that bee venom is worthy of further consideration.

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MECHANISM OF THE TOXIC EFFECTS FROM COMBINED USE OF CALCIUM AND DIGITALIS *

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THE administration of calcium with digitalis was considered a safe combination to enhance diuresis and to increase the effects of digitalis by Berhner,¹ Billigheimer² and Singer¹⁵. Recently, however, Bowers and Mengle⁴ reported sudden death in two patients who received calcium intravenously after previous administration of digitalis, and similar results were noted in animals that received a similar combination. Available experimental evidence points to either a synergistic effect or an additive phenomenon as the underlying factor for such untoward results. Lloyd¹ reported the electrocardiographic changes observed on himself during intravenous administration of calcium chloride, using first 50 c c of a 1 per cent solution and then a 10 per cent solution. No significant changes were observed during injection of the weaker solution but subsequent use of the 10 per cent solution resulted in cardiac standstill after but 4 c c had been given. Complete recovery followed when the injection was stopped at that point but this experience shows that intravenous injection of calcium is not always harmless. Walters and Bowler¹⁶ injected a 10 per cent solution of calcium chloride intravenously in dogs and found electrocardiographic evidence of changes in rate and conduction. Ventricular fibrillation was observed after toxic doses but therapeutic amounts resulted only in changes in heart rate. Billigheimer³ explains the change in rate as due to an effect on the vagus. Lieberman^{9,10} reported that intravenous injection of calcium produced effects closely resembling those produced by digitalis, namely, rise in blood pressure, slowing of the pulse, heart block, and various arrhythmias. This author^{10,11} believes that intravenous calcium produces an almost instantaneous digitalis-like effect on the heart while an interval of time is required for digitalis to act. He thinks that the result of both drugs given simultaneously or shortly after one another is merely additive. Billigheimer² thinks that calcium and digitalis act on the same structures of the heart but believes that digitalis sensitizes this organ to calcium. Similar observations were made by Mandelstamm¹³ and by Issekutz⁸. It is of interest to note that Edens and Huber⁶ found the blood calcium to be elevated when bigemini pulse appeared after digitalis and that Cushny⁵ reported less complete cardiac contractions after digitalis when the calcium content of the perfusion fluid in his preparations was reduced. Fischer,⁷ using isolated frogs' hearts, observed that calcium in the strength used in Ringer's solution, or in higher concentrations, had no effect if given before or during digitoxin administration but a marked calcium effect became apparent if

* Received for publication May 22, 1937

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digitoxin was employed before the calcium. He thinks that digitoxin sensitizes the heart to calcium but points out that this synergistic effect is one-sided, being effective only if digitoxin is given first. Schuntermann¹⁴ found greatly increased amounts of calcium in portions of dried myocardium in instances of cardiac hypertrophy with failure.

These differences in opinion as to the safety of the combined use of calcium and digitalis prompted us to reexamine the question in order to study the various factors and underlying mechanisms which may be responsible for the untoward results or death following this procedure.

PROCEDURE

Eleven dogs, each 8 to 12.5 kilograms in weight and anesthetized with sodium barbital, were employed. Digalen* was administered intravenously to the animals at a constant rate and in doses from 50 to 90 per cent of the calculated lethal dose (1.12 cat units per kilogram). After an interval of from 30 to 54 minutes 10 or 20 per cent solution of calcium gluconate was injected in the vein in five of these dogs. The quantity of calcium gluconate used did not exceed 20 per cent of the approximate lethal dose in any instance and the rate of injection was 4 c.c. or less per minute. Five other dogs received similar quantities of the two drugs simultaneously from the same syringe. The same precautions as to rate of injection and quantity of calcium were observed. Blood pressure variations were noted throughout each experiment. Electrocardiographic studies were made which included a three-lead control and repeated tracings of Lead II after each injection as well as prior to the death of the animal.

DISCUSSION AND RESULTS

The results are summarized in tables 1 and 2. In table 1 are shown the experiments where calcium gluconate was given 30 to 54 minutes after the digalen. The results obtained when the calcium gluconate and digalen

TABLE I

Experiment Number	Per Cent of Calculated Lethal Dose of Digalen	Calcium Gluconate	Time Interval	Result
1	85	15 c.c. 10%	30 min	Immediate death
2	66	25 c.c. 10%	36 min	Immediate death
3	60	11 c.c. 20%	54 min	Dog destroyed after 22 min
4	50	35 c.c. 10%	31 min	Death in 60 min
5	50	35 c.c. 10%	38 min	Death in 90 min

* We are indebted for the supply of digalen to Dr. L. Klein of Hoffmann-LaRoche and to H. Althouse of Sandoz Chemical Works for the calcium gluconate employed in these experiments.

were given simultaneously are shown in table 2. It will be seen that death occurred in both types of experiment with less than the calculated lethal doses of digalen, indicating that the calcium gluconate was in some way responsible for the greater effectiveness of digalen. Neither the rate of injection of calcium, which was constant in all experiments, the concentration or the total dose, which was never more than 20 per cent of the calculated lethal dose, could be responsible for death in some of the animals. Death of the animals and the time lag of its occurrence were found to depend on (a) the amount of digalen given, and (b) on whether the calcium gluconate was given simultaneously or at a short interval after the digalen. Both tables show that death occurred earlier with larger doses of digalen. It was also observed that death occurred earlier and was more likely to be

TABLE II

Experiment Number	Per Cent of Calculated Lethal Dose of Digalen	Calcium Gluconate	Time Interval	Result
1	83	17.5 cc 20%	0	Death 17 min
2	68	15 cc 20%	0	Living 28 min
	17	15 cc 20%	28 min	Death 2 min
	Total 85			
3	66	17.5 cc 20%	0	Death 50.5 min
4	50	17.5 cc 20%	0	Death 32 min
5	50	17.5 cc 20%	0	Living at 107 min
6	50	17.5 cc 20%	0	Living at 112 min

(1) 0 equivalent to simultaneous administration

(2) Dog 2 received a second dose of digalen (17 per cent of the calculated lethal dose) 28 minutes after the injection of calcium and showed no change for 28 minutes until another injection of calcium was given. Death then occurred in 2 minutes.

sudden with the same large dose of digalen if the calcium was injected about 30 minutes after the digalen. This, of course, is due to the time lag before the full action of digalen appears. In other words, in the simultaneous injections the calcium effect could have worn off considerably before the digitalis effect had become prominent. Nevertheless, it is significant that death sometimes occurred after a long interval when smaller doses of digalen were used. Apparently the effect of calcium gluconate may sometimes be more prolonged than is generally supposed.

The lag in death with smaller doses of digalen is in accord with some unreported results obtained by one of us (W. A. B.) with cats which indicated that intravenous injections of very large doses of digitalis resulted in toxic effects within a few minutes while comparatively small doses of digitalis required more time to produce comparable effects.

The present study indicates the hazard existing in the use of calcium gluconate intravenously following digitalis. Great caution should be used in patients who have received digitalis, especially if they show electrocardiographic or other evidence that they are digitalized. Even the simultaneous injection of calcium and digitalis in patients who have not previously received digitalis is not a harmless procedure. It is especially dangerous if larger doses of digitalis are given but untoward results may occur with smaller therapeutic doses. Our animal experiments suggest that the margin of safety in such combinations is both variable and narrow and that death may occur as late as one to one and one-half hours after injection.

Our experiments throw no light on whether death is due to additive phenomena or to a synergistic effect but it was observed that blood pressure rose shortly after injection of digalen in most instances to be followed by a precipitous drop before death after calcium was given. Electrocardiographic observations show the usual changes after large doses of digitalis, namely, changes in the T-wave and ST segment, heart block and ventricular tachycardia. Subsequent injection of calcium resulted in ventricular tachycardia and ventricular fibrillation. The latter mechanism was the cause of death in the animals who died immediately as well as in those who lived for as long as 90 minutes. Even those who survived developed ventricular tachycardia when digalen and calcium were injected simultaneously.

RÉSUMÉ

1 A series of experiments was performed to study the dangers and their mechanisms, inherent in administration of calcium with or shortly after digitalis.

2 We are in accord with previous observers who noted marked toxic effects or death when such combinations were used. These results could not be attributed to the digalen alone nor to the concentration, dose or rate of injection of the calcium.

3 The toxic or fatal effects depended on the size of the previous dose of digalen and depended a great deal on the time interval between injection of digalen and calcium. Toxic manifestations and death occurred when larger doses of digalen were used. These were more likely to occur if calcium was injected about 30 minutes after the digalen.

4 It was also observed that the margin of safety was narrow and uncertain and that the toxic effects following calcium, when digalen was given before, resembled those seen after very large doses of digitalis alone. Simultaneous injection of both drugs in similar dosage was somewhat less toxic and was less likely to be fatal than when an interval of about 30 minutes elapsed between the injection of digitalis and calcium.

5 Death in our animals was associated with a precipitous fall in blood pressure, and electrocardiograms revealed that ventricular tachycardia was frequent and that death was due to ventricular fibrillation.

6 The conclusion is reached that great caution is to be used in giving calcium intravenously with or shortly after digitalis. It is apparently not safe to use this combination even in patients who have received small doses of digitalis, but it is particularly dangerous if there is electrocardiographic or other evidence that the patient is approaching digitalization. We believe that it is wiser to abstain from intravenous injection of calcium in any patient who is receiving digitalis since the margin of safety is so narrow and the toxic effects can neither be foreseen nor successfully treated.

We are indebted to Messrs A C Meyer, Jr, and R Blake for technical assistance in these experiments.

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THE PRESENT STATUS OF RHEUMATISM AND ARTHRITIS· REVIEW OF AMERICAN AND ENGLISH LITERATURE FOR 1936`

(Fourth Rheumatism Review)

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* This Fourth Rheumatism Review was prepared by the Editorial Committee (Dr Hench, Chairman) of the American Rheumatism Association (formerly the American Association for the Study and Control of Rheumatic Diseases). The editorial comments express the opinion of the Editorial Committee, the authors of the Review, not of the Association.

† Dr Ghrist died February 3, 1937

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GENERAL INCIDENCE OF RHEUMATIC DISEASES, SOCIAL AND ECONOMIC IMPORTANCE

STATISTICS again demonstrate that the rheumatic diseases represent one of the world's greatest social and economic problems. Of all patients admitted in 1933 to accredited hospitals in the United States, 97,984 patients (1.39 per cent) were admitted because of "arthritis or rheumatic diseases" (Kling³¹³). A recent Public Health Survey (Collins⁹⁶) calculated the incidence of "chronic arthritis and rheumatic diseases" as 22.18 per 1000 persons, or 2.2 per cent of the population of which more than 1 per cent had "disabling" rheumatism and 0.85 per cent were "bedridden." (The morbidity rate for tuberculosis of all forms, including suspected cases, was only 4.72 per 1000, about one-fifth that of chronic rheumatism.) Based on these figures, Kling calculated that about 2,700,000 of the 120,000,000 population in the United States are affected with chronic rheumatic diseases, of whom 1,230,000 are "disabled" and 1,020,000 have been bedridden at some time or other. (Presumably the remaining 450,000 persons were affected mildly or moderately, not seriously enough to be "disabled" or bedridden—Ed.) Kling believes this to be a low estimate. According to the Massachusetts survey (1933),²⁴⁵ 3,264,000 persons or 3.2 per cent of the population of the United States suffer from chronic rheumatism.

The incidence of joint diseases in Finland is evidently less. In a house-to-house canvass of 37 rural communities with a population of 195,000 persons, Holsti and Rantasalo found 1702 persons (0.9 per cent) who had suffered or were suffering with "acute or chronic joint disease", of these 1177 had chronic arthritis, 525 had acute arthritis. Sex incidence of those affected was 2.4 females to 1 male, in acute cases 1.7:1, in chronic cases 2.7:1. The incidence of arthritis in different localities varied greatly from 0.3 to 4.3 per cent of the population, and was highest in southeastern Finland, on the coast of Lake Laakokka, where endemic struma is common.

CLASSIFICATIONS OF DISEASES OF JOINTS AND RELATED STRUCTURES

The editors of these reviews^{245, 246, 247} sympathize with Haden when he stated, "It is hopeless to discuss the different classifications or the different terms used to indicate the same *clinical type of pathologic process*." In the third review we therefore dismissed the year's crop of "new classifica-

tions" briefly since none seemed subject to less criticism than those in common use. A commission of the International League against Rheumatism has already collected more than 60 different nomenclatures. The ultimate classification of "rheumatic diseases" will be one based on a complete understanding of the etiology of the different forms. Until an etiologic classification can be completed it is necessary to use working classifications based on clinical data, pathologic or roentgenographic features or combinations thereof. None is entirely satisfactory but some have more merit than others. Because of the fundamental differences of opinion among the various schools of thought it is difficult to set up a nomenclature universally acceptable. But to avoid clinical confusions and for statistical purposes an international classification would be most helpful. To foster such a classification the International League against Rheumatism has asked committees in each country to simplify its own nomenclature to bring out the essential features of each disease-type. Cooperating in this work, a committee appointed by the American Rheumatism Association is critically reviewing major classifications now in use. This review will therefore not include critical comments on new ones proposed. Those interested in suggestions, amendments and criticisms of classifications in current use may consult the following references 4, 14, 129, 177, 183, 191, 223, 286, 318, 428, 476

DISEASES OF JOINTS RELATED TO TRAUMA

Trauma is related to articular disease in three ways: it may be the chief or sole cause of "pure traumatic arthritis", it may precipitate various types of arthritis, chief cause of which is some factor other than trauma, it may aggravate a preexisting active or quiescent nontraumatic arthritis. Campbell regards traumatic arthritis as the commonest type of joint affection.

(This may be true in the practice of an industrial surgeon or orthopedist but is not the experience of most physicians unless one regards as traumatic arthritis all three of the relationships listed—Ed.)

Articular Diseases Due Primarily to Trauma Three types of trauma produce articular damage⁷⁶: (a) A single mild or severe injury which damages articular structures with varying degrees of severity, (b) repeated occupational trauma from overuse and excessive wear and tear of joints, (c) repeated "microtrauma" from faulty posture or attitudes producing functional disability from unevenly distributed intra-articular pressure.

Symptoms The usual symptoms of pure traumatic arthritis result from the reaction of synovial, capsular or articular tissues to the irritative process⁷⁶. Traumatic arthritis is usually monarticular, rarely bilateral or polyarticular. Pain and slight swelling are generally present. Periarticular skin temperature, often increased in infectious arthritis, is usually normal in traumatic arthritis. On motion, crepitus may be present from a thickened capsule, synovial villi, or irregular articular surfaces. The joint may appear normal or effusion may occur. Large effusions may force articular

structures to assume abnormal positions which provoke muscle spasm and limited motion

Pathology Chief lesions produced are cartilage degeneration and, less notably, synovial fibrosis. There is early splitting of the cartilage matrix and subsequent fibrillation which may result in complete destruction of the cartilage of weight-bearing surfaces or of cartilage covering those surfaces affected by trauma (Ghormley and Deacon). These changes result because cartilage has little reparative powers. Marginal osteophytes appear later. The development of these changes has been reviewed (Campbell, Kling). Synovial hydrops is followed by formation of fibrin which may become organized into fibrous tissue adhesions. Synovial villi may increase in size and number. Beneath the synovia a fibrous tissue reaction occurs. Disease of cartilage produces no pain as sensory nerves are absent. When significant intra-articular hemorrhage occurs the synovia responds by hypersecretion, becomes thickened and inflamed. Blood is broken down, fibrin is precipitated and becomes organized with formation of adhesions.

Roentgenogram In the early stage of traumatic arthritis roentgenograms may be normal or may reveal subchondral osteoporosis. Later the hypertrophic changes and osteophytes are seen.

Synovial Cytology and Chemistry Normal synovial fluid contains about 10 to 200 nucleated cells per cu mm, and, according to Collins, a small, variable number of erythrocytes, from the trauma of aspiration. Only an occasional polymorphonuclear leukocyte occurs among the nucleated cells, 90 to 95 per cent of which are phagocytic cells resembling either monocytes of blood or macrophages of probable connective tissue origin. Collins studied the cytology of five traumatic effusions between seven and 51 days after injury. Variations in total and differential cell counts were as follows: erythrocytes, 200 to 25,000 per cu mm; total nucleated cells, 150 to 856 per cu mm; polymorphonuclears 2 to 32 per cent, lymphocytes 34 to 77 per cent, monocytes 9 to 18 per cent, macrophages 0 to 8 per cent, synovial cells 3 to 38 per cent.

In hemorrhagic traumatic effusions Kling found an increase of mucin, the presence of which increases the viscosity of the effusion. As a result of hemorrhage, the bilirubin content of the effusions may be increased for as long as six weeks after an injury. The icteric index of traumatic effusions is above 5, that of inflammatory effusions is invariably below 5. Other than trauma, only a few conditions (hemophilia, tabetic atrophy, xanthoma, sarcoma) cause spontaneous intra-articular bleeding and a high bilirubin content in effusions. The presence of fat in traumatic effusions distinguishes severe injuries from simple tears of joint capsule. If the fat is chiefly palmitin and stearin, it presumably originates from fat torn loose from fat pads and may indicate an injury to the intra-articular cartilages or to ligaments. If it is chiefly olein it must come from bone marrow, therefore its presence indicates intra-articular fracture. In such cases bone marrow cells may also be present in effusions.

SPECIAL FEATURES AND VARIETIES OF TRAUMATIC DISEASE OF JOINTS

1 "*Post-Traumatic Bone Atrophy*", "*Post-Traumatic Periarticular Fibrosis*" In 1900 Sudeck described an "acute post-traumatic inflammatory atrophy of bone" Since then considerable attention has been paid to the osteoporosis, but little to the associated periarticular fibrosis The cause of this osteoporosis is unknown but is presumably the result of a physiologic process which follows every toxic or traumatic irritation and is probably the result of an increased circulation to the part from vasomotor alterations initiated by the sympathetic nervous system Absorption of bone salts appears in roentgenograms as a "spotty atrophy" or mottling⁷⁶ It is differentiated from the atrophy of disuse, which is characterized by gradual encroachment of the marrow on the cortex and by diminution in the size of the entire bone

Post-traumatic bone atrophy may be painful In one case Ghormley noted atrophy of cartilage Gordon regarded the bone atrophy as secondary to the earlier periarticular fibrosis Following an injury or fracture of an extremity, swelling and a soft pitting edema distal to the lesion may appear and persist Joints of hands or feet may become painful and stiff due to proliferation of periarticular fibrous connective tissue Subsequent decalcification of bone occurs Lymph stasis supervenes, later the vascular content of subcutaneous tissues is apparently reduced Overgrowth of periarticular connective tissues occurs, limitation of motion and pain are present, contractures and protective muscle spasms ensue, and atrophy results In severe cases roentgenograms show decalcification of bone, slight thickening of periarticular tissues, narrowing of joint spaces If the original injury or fracture is near the torso, this condition is less likely to affect hands and feet because collateral circulation of blood and lymph distal to the original injury is generally adequate

The condition is avoided by preventing or correcting capillary and lymph stasis Only that part of the extremity for which rest is vital should be kept at rest Rings should be removed Dressings should not be constrictive Adequate, protective cotton pads should be used with splints and the latter should be temporarily removed to permit massage if swelling appears Frequent elevation of affected extremities is important Usually the condition clears satisfactorily, occasionally it is protracted In severe cases one or two toes or fingers may become ankylosed Relief was obtained in two cases treated by White with procaine injections of sympathetic ganglions

Apropos of these statements is Jones' interesting review of the conditions which foster articular adhesions with injury or disease

The following questions were raised and answered by Jones Why may joints sometimes be immobilized without becoming stiff, whereas at other times dense adhesions form although joints have not been completely immobilized? Why can some joints be immobilized for a year with impunity, and others become permanently stiff within a few weeks? Why is the wrist joint more likely to become stiff when immobilized in a cock-up splint and not in a dorsal plaster splint? Why do massage

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and passive stretching always aggravate stiffness of finger and elbow joints? Joint adhesions from injury are generally formed, not in intra-articular or interarticular, but in periarticular, tissues. Stiffness results from periarticular adhesions in the plications of joint capsule. Adhesions arise from organization of periarticular sero-fibrinous exudate which provides the adhesive substance responsible for the gumming together of adjacent tissues. First a fibrinous deposit occurs, later fibrin is replaced by young connective tissue, ultimately by fully formed fibrous tissue. When traumatic (or infectious) synovitis occurs, or when the joint capsule is torn, exudate is poured out from synovia or from torn edges of the capsule. Even though the joint is normal, periarticular adhesions may form as a result of certain extra-articular conditions: a spreading exudate from distant injury or infection, recurrent edema of juxta-articular tissues, simple venous stasis and congestion due to muscular inactivity of immobility and disuse. The potency of these factors in promoting adhesion formation depends on the degree of exudation, the fibrin content of the exudate and the frequency with which the soaking is repeated. The recurrence and persistence of serofibrinous exudation provide the key to adhesion formation. If articular tissues are soaked in exudate, day by day, adhesions will form whether immobility is complete or incomplete and whether the joint is injured or normal. If injury is not repeated, even a severe fracture of an elbow joint will cause less adhesion formation than the relatively trivial injury of passive stretching repeated day after day by an overenthusiastic masseur. Adhesions form less readily about an ankle joint immobilized in a walking plaster cast than about the same joint left free to move but subject to recurrent edema. "Edema is the glue from which adhesions are made" (Not ordinary edema, but that from inflammation and trauma—Ed.)

2 *Pellegrini-Steda Syndrome* When the medial collateral tibial ligament of a knee is traumatized a peculiar reaction may occur therein: bone may be formed in the ligament. This is the Pellegrini-Steda syndrome, recently described in American literature (Kulowski, 1933). Two cases were reported (Henson). Each involved a history of recurrent trauma, swelling of the knee and pain on motion. Roentgenograms revealed the condition. Surgical procedures used in treatment were outlined.

3 *Tennis-Elbow* There is no unanimity of opinion concerning the basic pathology or the optimal treatment of "tennis-elbow." According to Cyriax, it is caused primarily by a tear between the tendinous origin of the *extensor carpi radialis brevis* and the periosteum on the anterior surface of the lateral epicondyle, a chronic periostitis results secondarily and to this symptoms are referable. Cyriax described his method of treatment which gave "complete and lasting relief": repeated deep friction to the tender area, followed by forced adduction of the extended and supinated forearm.

Medicolegal Aspects of Traumatic Arthritis Data considered necessary by some to determine the presence of traumatic arthritis and to assess the degree of disability therefrom have been given^{245, 247}. It was stated that, in addition to other data, one should have information on the time between injury and onset of symptoms, it should not be more than a few months to a year. Some disagree on this last point. According to Henry the injury must be severe enough to cause immediate cessation from work and symptoms must appear immediately (or within a few days) after the accident and persist continuously. According to Lecklitner "bridge symptoms"

must be present, that is, the symptoms (to be caused by traumatic arthritis) must have continued uninterruptedly from the time of trauma to the onset of arthritis, and other joints of the body must be free of arthritic lesions

Nontraumatic Arthritis Precipitated by Trauma Mild trauma may instigate or precipitate an arthritis (atrophic or tuberculous, or that from syphilis, pyogenic infections or neoplasms) the chief cause of which is some factor other than trauma In a gouty patient mild trauma may initiate a severe attack of gouty arthritis, out of all proportion to the degree of trauma which provoked it (Campbell, Kling)

Nontraumatic Arthritis Aggravated by Trauma Any preexisting arthritis (most commonly hypertrophic, senescent or degenerative osteoarthritis) may be aggravated by trauma In patients with previously asymptomatic, senescent hypertrophic arthritis trauma may induce persistent symptoms In such cases the medicolegal question arises how much disability is attributable to trauma and how much to the previously existing disease? ⁷⁶

In three patients Epstein noted results of severe trauma to joints ankylosed from previous disease Fracture occurred not at the site of ankylosis but in adjacent, thinner para-articular bone Hence a completely welded, eburnated articulation of two long bones of an extremity, that is, a true ankylosis, is a mass of bone of greater strength than that of nearby "healthy" bone

TREATMENT OF TRAUMATIC ARTHRITIS

Current treatments are as previously outlined in the first three reviews Aspiration of traumatic effusion evacuates pathologic products from joint cavities and reduces inflammation (Kling) Henson inflated joint cavities with oxygen to prevent and to "break up" post-traumatic adhesions (also those from infection) Weight bearing and physiotherapy were used in addition to oxygen inflations Motion of joints was restored more readily and more painlessly by this combination than otherwise Pain was generally decreased and manipulation of joints avoided

Histamine ionization was advocated (Mackenna) Short wave therapy was used by Speeding

(Evidence proving the superiority of these measures was almost wholly lacking in these reports—Ed)

"GONORRHEAL RHEUMATISM" GONORRHEAL ARTHRITIS

Incidence In the United States 700,000 persons apply annually for the treatment of acute gonorrhea (Barney) According to Usilton (1935) about 500,000 patients in the United States are constantly under treatment or observation for gonorrhea Considering those with gonorrhea who never report for treatment it has been estimated that between 1,000,000 and

2,000,000 new infections with gonorrhea occur yearly in this country (Thomas and Bayne-Jones, Barney) About 3 to 5 per cent of persons with gonorrhea are said to develop gonorrheal arthritis of varying severity A much lower incidence is reported from Johannesburg, South Africa of 6000 patients with gonorrhea, 30 (0.5 per cent) developed gonorrheal rheumatism (Bayer)

Clinical Features Reviewing the clinical features of gonorrheal arthritis Warren stressed certain points A careful history usually reveals transitory involvement of many joints for several days at the onset, then the acute major involvement, generally of one but not infrequently of several joints or near-by structures Often the process subsides in one joint and flares up successively in other joints, particularly in a previously traumatized joint In some cases the process is restricted entirely to tendon sheaths or bursae around a joint or to nearby muscles and fascia A notable feature is the rapidity with which the acute arthritis and bone and muscle atrophy progress

Gonorrheal arthritis in children is rare In one series of cases it occurred in 1.5 per cent of children with gonorrheal vulvovaginitis (Gittings and Mitchell, 1917) Su and Hu noted severe gonorrheal polyarthritis in a girl aged four years who had apparently contracted the disease from recently infected parents The child developed vulvovaginitis, fever, adenopathy and arthritis in three joints Although treatment was chiefly symptomatic, articular recovery was complete

(It often is if organisms do not invade the articular cavity—Ed.)

The simultaneous occurrence of gonorrheal arthritis in a mother and a newborn infant is rare, an instance is reported by MacLennan Infants with gonorrheal ophthalmia may develop arthritis between the fifth day and the fifth week, generally the second week, of infection Although infants with severe ophthalmia may die, prognosis regarding joints is usually good

Most cases of persistent gonococcemia are fatal Among the 27 cases of nonfatal gonococcal septicemia without endocarditis reported in the literature two patients had erythema nodosum An additional case was reported by Bakst, Foley and Lamb

Pathology The "classical type" of reaction occurs when articular tissues are directly invaded by gonococci There is an inflammatory synovial reaction with infiltration of leukocytes, lymphocytes and macrophages In synovial exudates are found gonococci and inflammatory cells, especially leukocytes Jordan regarded as unproved the existence of a "second type" of gonorrheal arthritis in which gonococci are not found in articular and peri-articular tissues to explain the inflammation therein Some suppose that such a type represents an "allergic gonorrheal arthritis," a sensitization of joint tissues to metabolic products of distant gonococci According to Ghormley and Deacon, the pathologic reaction in gonorrheal arthritis is essentially similar to that of other pyogenic forms of arthritis synovial

thickening, edema, polymorphonuclear leukocytic infiltration, later the production of fibroblasts and capillaries, infiltration by plasma cells and polymorphonuclear leukocytes, and still later the advanced stage of synovial fibrosis. Differences in reaction depend largely on the number and virulence of the organism and the patient's resistance.

Roentgenograms In acute gonorrheal arthritis roentgenograms present no special characteristic except perhaps the early and unusual, diffuse character of the atrophy and the marked, often rapid, bone destruction (Warren). Taylor and his colleagues regarded this feature as of considerable diagnostic value to clinicians. The appearance of a gonorrheal joint of six weeks' duration may closely resemble the appearance of a joint with tuberculous involvement of six months' duration. To suggest a diagnosis of gonorrheal arthritis, therefore, a roentgenologist should know at least the duration and severity of articular symptoms. Studying roentgenograms in 11 cases, Taylor and associates noted marked variations at different stages of the disease. In the "early stage" marked soft tissue swelling appeared early and subsided within a few days or weeks. Local areas of decalcification and slight effusion were each noted in 64 per cent of these cases. Later these both decreased. Later still there was narrowing of joint spaces in 82 per cent, a moderate degree of "active bone destruction" in 36 per cent, early healing with fibrous or bony ankylosis in 45 per cent.

Laboratory Data A certified diagnosis of gonorrheal arthritis can be made only on recovery of gonococci from articular tissues or fluid. This is generally not done. A reasonably accurate presumptive diagnosis of gonorrheal arthritis is usually made on the basis of certain clinical data supported by laboratory evidence of the presence of urogenital gonorrhea. The elaborate report by Thomas and Bayne-Jones of the Committee for a Survey of Research on the Gonococcus and Gonococcal Infections contained much data of interest to clinicians: data on the biology of gonococci, on types of gonococcal infections, on the relative value of different methods of treatment of gonorrhea and on the respective merits of laboratory tests used in diagnosis.

1 Isolation of Gonococci in Smears and Cultures Although in most cases of acute gonorrhea in males a diagnosis based on examinations of stained smears from secretions is probably correct, such a diagnosis is not free from uncertainty. Recent literature reflects a growing sentiment against relying on smears alone for diagnosis (Thomas and Bayne-Jones). Although opinions differ as to the relative value of smears or cultures for isolating gonococci, most workers now favor cultures. Warren's experience indicated that smears from urogenital discharges may be positive for gonococci in 40 per cent, cultures of such discharges may be positive in 60 per cent, and cultures of articular tissues may be positive in 80 per cent of cases in which gonorrhea is suspected. These percentages are higher than those of others. Leahy and Carpenter found the diagnostic value of smears slightly greater than that of older cultural methods but when they used a modification of McLeod's new (1928-1934) method the reverse was true. Ten per cent more positive cases of gonococcal infections were discovered by the new cultural method than by the smear method alone. Smears were positive in 45 per cent, cultures positive in 55 per cent of cases studied, in 13 per cent cultures were positive when smears were negative or doubtful, in 2

per cent cultures were negative but smears were positive. Similar results were obtained by Spohr and Landy, using another modification of McLeod's method. A study of material from male urethras gave the following results: Smears and cultures were both negative in 22 per cent of cases examined, smears were negative but cultures were positive in 10.3 per cent, smears were positive but cultures were negative in 7.7 per cent, both smears and cultures were positive in 60 per cent. The superiority of the cultural method was more notable in tests on material from suspected females. In studies of urethral secretions smears and cultures were both negative in 52.5 per cent, smears were negative but cultures were positive in 10.2 per cent, in no case were smears positive and cultures negative, in 37.3 per cent both smears and cultures were positive. Studies of cervical secretions revealed negative smears and cultures in 49.2 per cent, negative smears and positive cultures in 3.2 per cent, positive smears and negative cultures in none, positive smears and cultures in 18.6 per cent. Thus, in the latter group smears were positive in 18.6 per cent but cultures were positive in 50.8 per cent.

2 Gonococcal Complement-Fixation Test Further experiences with this test indicated that, properly interpreted, it is of diagnostic value. For the test to be positive, enough antigen must be absorbed to stimulate the formation of sufficient antibodies to produce the reaction in blood and a period of time sufficient for the development of the reaction must have elapsed. In mild or 'subacute' (as contrasted with acute) cases, or in those in which discharges are open and draining freely, and in which but little antigen is absorbed, the test may remain negative despite the presence of definite gonorrhea. The current reports of Warren, Pelouze, McEwen, Alexander and Bunim, Hirshland and Hirshland and Lin have restated the characteristics of the test. 1 The test may be negative the first two to six weeks of infection. 2 It may require 4 to 20 weeks for complete fixation to occur. 3 Tests should be repeated, especially if the first ones are negative. A positive test was frequently not obtained by McEwen and associates until the third bleeding. 4 Some²⁶⁵ regard a repeatedly weak-positive reaction as specific as a (single) strongly positive reaction (Others do not agree to this—Ed). 5 The test is more frequently positive in acute systemic infections (such as gonorrheal arthritis) or in chronic infections than in acute local infections. 6 Repeatedly negative tests are strong presumptive evidence against the presence of gonorrhea. 7 After patients have clinically recovered the test may remain positive for many months (as long as four years—Warren), therefore it is of little value as an immediate proof of cure. 8 The test generally becomes negative within 6 to 18 months after clinical recovery. 9 A persistently and markedly positive reaction in a case of presumed arrested gonorrhea strongly suggests the presence of a (hidden) active gonococcal focus³⁴⁴.

Results of the test confirmed the clinical diagnosis in 76.4 per cent of the cases of Hirshland and Hirshland who found it particularly useful in females from whom it is difficult to obtain positive pelvic smears. Of 44 patients with gonorrheal arthritis seen by McEwen, Alexander and Bunim, 98 per cent gave a positive reaction: 4 plus in 20 per cent, 3 plus in 33 per cent, 2 plus in 36 per cent, 1 plus in 2 per cent, doubtfully positive in 7 per cent. False positive reactions were found in no normal controls but in several pathologic controls: in 2 per cent of 48 cases of osteoarthritis, in 3 per cent of 39 cases of atrophic, in 3 per cent of 36 cases of miscellaneous arthritides, in 7 per cent of 70 cases of rheumatic fever. Some of the latter patients had rheumatic polyarthritis and coincidental urogenital gonorrhea.

Lin tested the sera of 500 persons, 323 with active or arrested gonorrhea and 177 with nongonococcal infections used as controls. Of the control cases 3 per cent gave false-positive reactions. The reaction was falsely negative in 25 per cent of the cases of gonorrhea proved active by smears. Of 187 specimens representing cases of active gonorrhea, smears and serologic reactions were both positive in 95 cases, smears alone were positive in 31 cases, the serologic reactions alone were

positive in 33 cases. Complement-fixation tests generally became negative in less than 6 months after patients were clinically cured.

According to Thomas and Bayne-Jones the present status of the test is as follows. In spite of technical improvements it still remains one which cannot be satisfactorily done by a poorly trained or indifferent technician, and is one which exhibits, even when skillfully performed, vagaries whose conquest will demand time and research. Variations of materials and procedures used for the test have been so numerous that they defy classification. Various antigens, solutions, autolysates and protein-fractions of the organism are used. A greater standardization of technic is necessary and the most reliable antigen must be found. Despite all this the weight of evidence conclusively shows the specificity and considerable diagnostic value of the reaction.

Koopman and Falker devised a "more sensitive and quantitative" method for the test, one which does not give false-positive or indefinite reactions except in cases of meningitis. (No results with the test were tabulated—Ed.)

3 Skin Tests Although some workers regard skin tests with various products of gonococci as of diagnostic value, there is no general agreement on their worth.⁵⁴³ Conrad used the Corbus-Ferry filtrate and a control solution for skin tests on 50 cases with no history of gonorrhea, and on 50 cases with clinical and laboratory evidence of gonorrhea. Forty-eight hours after injection, 98 per cent of the 50 gonorrheal cases demonstrated a skin reaction averaging 2.3 cm. as compared to reactions averaging 0.2 cm. in the control cases. No false-positive or negative reactions were noted. According to Corbus, the mechanism of skin reactions to the Corbus-Ferry filtrate is due to allergy.

4 Synovial Cytology The cytology of 5 specimens of synovial fluid in 2 cases of gonorrheal arthritis of "considerable chronicity" was noted by Collins. Total nucleated cells varied between 5,200 and 23,400 per cu. mm., polymorphonuclear leukocytes, between 30 and 77 per cent.

Treatment This includes the management of the primary focus, that of the infected joints, and general treatment. Although fever therapy is being more widely used to heal both the local genital and articular disease, older methods are used by many. Stressed were the importance of early treatment even in mild cases, bodily rest to prevent systemic invasion, strict avoidance of trauma to genital tissues from the over strenuous use of instruments, massage and strong chemicals, avoidance of sexual and alcoholic stimulation, and the choice of various urinary sedatives and urethral medicaments.^{26, 30, 169, 402, 429, 543}

Local applications of different chemicals and the use of vaccines found little favor with Thomas and Bayne-Jones. When chemicals are strong enough to affect bacteria they generally irritate tissues. Most specialists in the United States question the usefulness of vaccines except perhaps in chronic or complicated cases. The manifold preparations made from gonococci and used as vaccines "indicate that none fulfills all requirements. After all in the present state of knowledge concerning the clinical composition of the organism and its metabolic products preparing them is like shooting in the dark."⁵⁴³ Several, however, favored the use of Corbus-Ferry filtrate. With it James "cured" 20 of 34 cases and Jamieson "cured" all of 9 cases of acute or chronic gonorrhea.

(Data on controls were not given—Ed.)

Corbus believed that the filtrate prevented complications, they occurred in only 3 per cent of 175 cases, arthritis never developed. In cases treated otherwise, when arthritis appeared it frequently yielded "completely in an exceedingly short time" with the use of filtrate and prostatic massage.

Others consider the filtrate valueless. The results of McKenna, Goldfader and Fishberg in the treatment of 34 cases of gonorrhea with routine treatment plus the filtrate were no better than those treated only routinely. Complications were not prevented. Spence obtained "uniformly poor results." Miller's³⁶⁷ results with filtrate were "not remarkably better" than those obtained otherwise. Deakin's patients with acute gonorrhea did not do so well with the filtrate as without.

Bertoloty and Herraiz considered Loeser's (1930) method of producing active immunization by injections of live gonococci superior to classical vaccine therapy.

The treatment of the joints includes rest with the appropriate type and amount of immobilization, physiotherapy and analgesics. According to Hamilton, amiodoxyl (ammonium o-iodoxybenzoate) has a profound effect on the pains of gonorrheal arthritis although it is useless in atrophic or hypertrophic arthritis. He compared results in 38 patients with gonorrheal arthritis treated therewith to those in 30 patients treated with ordinary methods. Amiodoxyl relieved pain, shortened the period of disability and reduced the percentage of permanent disability more effectively than any other generally used treatment. Of those treated with amiodoxyl, 69 per cent were "cured," 18 per cent improved, 13 per cent unimproved. Of the control group only 7 per cent were cured, 37 per cent were improved and 56 per cent unimproved. (Results in the controls were worse than usually reported—Ed.) The drug, given intravenously, may produce toxic manifestations, fever, erythema, vomiting, diarrhea, headache, when these occur its use should be promptly and finally discontinued or there may be a fatal result. Death occurred in one of Hamilton's cases and in five others noted in the literature.

(The reader cannot form an independent opinion from Hamilton's papers. Only meager details of his cases were given. His charts were difficult to interpret. The control group was apparently not comparable to that treated with the drug, 20 of the 30 control cases were of chronic, only 10 were of acute, arthritis. The analysis of the control group was "very incomplete because of lack of chart data." The value of the drug remains to be proved. It must be remembered that many cases of "gonorrheal arthritis" represent a transient polyarthralgia and disappear spontaneously—Ed.)

Gold therapy was used by Slot and by Oren.

Aspiration, drainage and irrigation of joints were advised in severe cases.^{231, 238, 297} Aspiration may relieve pain, protect intra-articular tissues from material which would destroy cartilage, prevent undue capsular stretching and reduce the formation of adhesions. If a large joint is involved and aspiration of synovial fluid reveals much fibrin, marked synovial leuko-

cytosis (more than 40,000 leukocytes per cu mm) and gonococci, Keefer favors irrigation through a small incision in the capsule. Burman devised an aspirating syringe with a side-cock adapter for injecting air into gonorrheal (and other) joints with effusion. Restorative treatment for joints includes the use of physiotherapy, protection of arches weakened by long rest, and procedures to correct flexion deformities or ankylosis.

For general debility blood transfusions and a liberal food intake were advised.²⁹⁷

Fever Therapy None of those advocating the measures just described apparently used fever therapy or compared its results with those of other methods. The parade of experience with fever therapy has continued to provide further evidence of its superiority over other methods.

Bierman and Levenson noted further results of systemic heating plus additional focal heating. The patients' temperatures were first elevated by means of a hot bath and cradle of lights to about 105° F (rectal). Then the pelvic temperature was further elevated to about 111° F by pelvic (rectal or vaginal) diathermy electrodes. Sixteen patients with gonorrheal arthritis were given two to six fever treatments, each three to five hours in duration, about twice weekly. The previous duration of gonorrhea was 4 to 28 (av 12.8) weeks, of the arthritis, 3 to 25 (av 10.2) weeks. Most of the patients had previously been treated ineffectively by other measures. Two already had ankylosis. Complete restitution of articular function was obtained in 13 of the 16 patients, partial restoration in one and very little in the two with ankylosis. Bierman also reported excellent results in the treatment of 52 cases of gonorrhea in females, in 26 of which salpingitis was present. In 45 of the 52 cases the cervix and urethra were sterilized after an average of 2.4 treatments per patient, 15 of the 45 patients required only one treatment.

Stecher and Solomon considered fever therapy practical, safe and satisfactory in the hands of experienced attendants. It provided cure or marked relief in a high percentage of cases and saved much time from disability. Fifty cases of gonorrheal arthritis were treated in the Kettering hyperthermia, generally at 107° F for five hours⁵¹⁶; 54 per cent were "relieved of all joint symptoms," 22 per cent were benefited and 26 per cent were not helped. Of the 50 cases, 41 were of acute arthritis (10 weeks' duration or less), nine were of chronic arthritis. Complicating conjunctivitis and uinitis were promptly cured. Genital infections were generally but not always entirely cured.

Slaughter and Trautman, and Trautman with a Kettering hyperthermia treated 25 patients with acute gonorrheal arthritis. 16 "recovered completely," five improved markedly, four moderately. Fifteen patients with chronic gonorrheal arthritis were also treated; ten recovered completely, three were markedly improved and two were not improved. Genital infections were cured concurrently in 22 of the 25 acute cases, in 14 of the 15 chronic cases.

Twenty-nine of Simpson's 31 patients with acute arthritis (of less than eight weeks' duration) and seven of 14 patients with chronic arthritis recovered "complete joint function" Marked articular stiffness persisted in two chronic cases in spite of fever therapy but was relieved by orthopedic manipulation under anesthesia followed at once by fever therapy Urogenital infections were completely cured in 38 of the 45 cases, soon disappeared spontaneously in four others, but two patients who had insufficient fever needed additional treatment

Of McClure's 16 patients with acute or chronic gonorrheal arthritis, nine were "cured," four improved, three stopped treatment prematurely "In some instances there was complete or almost complete relief from symptoms following the first treatment and from the experiences with these patients it is very definitely felt that fever therapy alone is often sufficient to effect a complete cure" For chronic cases supplementary physiotherapy was advised

Using a "hot box" alone Gurnee cured only 55 per cent of his cases of gonorrhea in females Treatments were strenuous and unsatisfactory Thereafter patients were treated in the "hot box" with additional pelvic heating by the Elliott method, oral temperatures being kept at 105° F, the water in the vaginal bag was at 115 to 118° F Thus, higher rectal temperatures were obtained in the presence of moderate cerebral temperatures and heat stroke was avoided All of five cases of gonorrheal arthritis were improved 90 to 95 per cent Their hospitalization was reduced 75 per cent of that necessary by older methods The combination of Elliott and "hot box" treatments seemed safer than that of Elliott treatments plus short wave diathermy, which Gurnee also tried

Fourteen of Owen's 22 patients with gonorrheal arthritis were "cured" by an average of 4.8 periods of fever of 4.6 hours each Eight patients who only averaged 2.8 periods of five hours each were improved, not cured, failures were due to insufficient heating "Given patients who can and will take the treatment, better than 80 per cent of gonococcic infections regardless of complications may be absolutely cured in the space of two weeks

This progress in therapy is most appreciated as it applies to arthritis, formerly so painful, time consuming and often permanently disabling" Ability to take treatments depended on the condition of the heart, the resistance of the skin to heating and the patient's temperament For one reason or another 12 per cent of Owen's patients were unsuitable for fever therapy

A summary of published results from the treatment of 151 cases of acute gonorrheal arthritis and 32 of chronic arthritis was made by Hensch

(This also appeared in the third review—Ed.)

General Remarks on Fever Therapy The institution of fever therapy is not a simple matter to be done in a physician's office by a physician or nurse not specially trained in the technic It is a highly technical procedure which demands as much care as that required for a surgical operation

Even in the hands of a well trained personnel complications will occasionally occur, generally they are mild, but sometimes they are serious. Several papers included details on the management of patients under treatment, the contraindications, physiologic effects and complications^{12, 39, 41, 140, 141, 198, 219, 317, 385, 400, 418, 492, 510, 524, 541, 550}. The whole subject was extensively discussed in Neymann's review of 332 reports. Other reports noted the beneficial effect of fever therapy in gonorrhea uncomplicated by arthritis^{131, 140, 141, 362, 400, 494, 524}.

Contraindications to fever therapy were listed: advanced age, cardiovascular or renal dysfunction, chronic alcoholism, pulmonary tuberculosis, marked debility or emotional instability^{140, 141, 418, 524}. The hazards of fever therapy must not be overlooked. Certain patients are brought to the borderline of disaster by degrees of fever not tolerated by them. For details concerning the hazards, complications and accidents incident to fever therapy reference should be made to the reports cited. As Trautman stated, gonorrhea is not a mild disease, it can cause great disability, suffering and economic loss. Therefore the use of fever therapy is justified in spite of occasional failures or disasters. Trautman had experienced no fatalities in the treatment of 238 patients with 1383 fever sessions. Simpson noted no serious complications from 3204 fever sessions given to 431 patients.

(Warren, Scott and Carpenter noted one death in the treatment of 283 cases of gonorrhea in six years. At The Mayo Clinic one death occurred in connection with about 4500 fever sessions given to about 600 patients—Ed.)

Complications of fever therapy include first degree burns and cutaneous vesicles, diffuse erythema, occasional constipation, diarrhea, anorexia, nausea, headache, herpes labialis, dehydration and exhaustion, tetany, circulatory failure and heat stroke from loss of chlorides and cerebral hyperthermia. One of Stecher and Solomon's patients developed a severe, and two a mild, epileptiform seizure. When Gurnee used the "hot box" alone one of his 27 patients died of heat stroke and two developed severe heat stroke, but no serious effects were noted among his 30 patients treated by combined relatively low general and high pelvic temperatures.

(Details of the instance in which the patient died were not given—Ed.)

One of Stein's patients with gonorrheal arthritis responded well to two fever sessions, but about 12 days later signs of pyramidal tract involvement were noted which disappeared in two weeks. Three hundred thirty-one episodes of delirium were suffered by 108 of the 200 patients of Barnacle, Ewalt and Ebaugh who had a total of 1324 fever sessions. 204 of the episodes were mild, 118 moderate and nine severe. Delirium averaged 75 minutes (max 48 hours) and generally occurred in the first fever session. Large, but not small, doses of sedative drugs seemed to predispose thereto.

Additional reports of interest were of the following: electrocardiographic

changes in artificial fever⁵⁵⁴, velocity of blood flow in artificial fever^{318, 319}, effects of fever therapy on blood count, blood and urine chemistry^{118, 190}, temperatures of superficial and deeper tissues during hyperpyrexia⁴⁶³, the relative efficiency of various methods for producing fever^{244, 327}, a "satisfactory cheap device" for fever production¹³. The Therma-mode blanket was deemed not acceptable for use in fever therapy (Council on Physical Therapy of the American Medical Association)

Criteria of Cure of Gonorrhea These included the following disappearance of clinical signs of disease and of discharges, presence of clear urine without shreds, absence of gonococci in the shreds when these latter are present, two or three negative smears and cultures, presence of a prostate of normal consistency, prostatic secretion free from leukocytes, absence of urethral flare-up after sexual excitement or after alcohol, in women the presence of no visible cervical irritation, no tubal thickening or tenderness, no flare-up after menses (Brodie, Owens, Pelouze)

Prognosis, End-Results Spontaneous remissions of gonorrheal arthritis may occur with little residual damage "in a fair percentage of cases" (Warren). Certain patients even with gonococcemia may recover under symptomatic treatment alone (Su and Hu, Bakst, Foley and Lamb). However, the chances of residual articular damage are too great to neglect thorough treatment. Kuhns regarded the course of chronic gonorrheal arthritis (untreated by fever therapy) little different from that of other types of chronic arthritis.

(Many believe the term "chronic gonorrheal arthritis" should be restricted to indicate the past history and not to imply a forecast of progressive disease. The term should be used only to indicate that articular symptoms have already existed six weeks or more but not to signify that there is present a chronic progressive arthritis with prolonged symptoms of active inflammation. Gonorrhea rarely (if ever) produces chronic articular disease which progresses independently unless repeated infection or chronic trauma occurs—Ed.)

TUBERCULOUS ARTHRITIS

Clinical Data Current reports include several useful reviews. According to Henderson, the disease is less frequent because of better control of the milk supply and the education of the public on prevention and treatment. Nevertheless, Dickson stated that tuberculous arthritis is responsible for about 20 per cent of all the cripples in the United States. (The basis of this estimate was not given. It seems much too high—Ed.)

Dickson distinguished between tuberculous monoarthritis (the usual variety), multi-articular tuberculosis (tuberculosis may affect three or more joints in about 5 per cent of cases) and tuberculous polyarthritis or "tuberculous rheumatism" (which will be discussed separately). Tuberculous arthritis can be divided into two stages. 1. The early synovial or pseudosynovial, "preroentgenographic" stage, when the disease is roentgenographically invisible and no osseous foci are obvious, 2. A later stage when more or less definite roentgenographic changes are present.

Early symptoms include Generally an insidious onset, slight swelling or pain or both, sometimes merely stiffness, local warmth, a limp if the joint bears weight Constitutional symptoms may be absent or slight loss of weight, a little fever As the disease progresses the cartilage becomes eroded, the bone is exposed, pain and stiffness increase and affected children give night cries or there is jerking, especially in hips and knees, from contact of affected bone ends when muscles relax With progressive bone destruction abscesses may form with or without fever, depending on the occurrence of secondary pyogenic infection If synovia alone is affected, as occurred in 9 per cent of Henderson's cases, symptoms are chiefly stiffness and swelling If bone is primarily affected, as is usual, symptoms depend on the situation and size of abscesses They may exist for years, causing little discomfort If they break through into the joint abruptly, acute "panarthritis"—involvement of all structures of the affected joint—results Usually abscesses break through gradually and barriers of protecting adhesions are built up at the site

In Dickson's 158 cases of tuberculous arthritis, joints involved were as follows spine in 62, hip in 41, knee in 25, ankle in 11, wrist in 10, sacro-iliac in 6, shoulder in 2 and elbow in 1 case

Multiple arthritis occurred in six of Dickson's 158 cases the spine was involved in two places once, the spine and knee in two cases, the spine and both hips once, and the knee and wrist, and hip and wrist once each The tuberculous, or unusual, nature of the polyarthritis was suggested by its asymmetry and the successive, not coincident, involvement of the several joints

Rare features of tuberculous arthritis are perforation of abscesses of the hip joint, sequestration of parts of the femoral head into the bladder and lengthening of a leg due to stimulation of growth centers by increased vascularity (Henderson) Armstrong noted tuberculosis in a joint which was the site of exostoses typical of metaphysical aclasis, and the presence of extensive tuberculous synovitis in a joint without appreciable stiffness, pain or deformity and without roentgenographic bone changes or pathologic (biopsy) involvement of articular cartilage or bone

Pathology The usual synovial reaction was described (Ghormley and Deacon)

From a study of four postmortem specimens Compere and Garrison concluded that tuberculous spondylitis begins in cancellous vertebral bone and encroaches on vertebral cartilage and intervertebral disks Cartilage and *annuli fibrosi*, being resistant to tuberculous invasion, persist longer than bone As the disease progresses bone is destroyed by the extension of tuberculous tissue which may or may not contain typical tubercles The anterior common ligament is elevated from the vertebral bodies, the disease extends along the spine beneath this longitudinal ligament, involving vertebrae above and below but not the disks until late Abscesses may push back into the vertebral canal but do not tend to penetrate dura The tuberculous processes were compared to those in osteomyelitis

Vertebral osteomyelitis also seems to begin in cancellous bone via hematogenous implants, as Compere and Garrison noted, it could hardly begin in disks since they

contain no blood or lymph vessels. In contrast to their fate in tuberculous spondylitis, disks in osteomyelitis are quickly destroyed and formation of new bone and vertebral fusion may occur. When tuberculous spondylitis is complicated by pyogenic infection the pathologic reaction is mixed, new bone formation from the pyogenic infection is associated with tuberculous bone destruction.

A case of extensive tuberculous spondylitis which healed under conservative treatment supplied Finder with interesting pathologic material when the patient finally died. The destructive bone changes and osteoporosis, so common in the active stages of tuberculosis, were absent. Bone lesions had healed and osteosclerosis had developed, complete union by bony fusion had occurred between two vertebrae. Finder concluded that healing may occur spontaneously, and vertebral bone sclerosis, as seen in roentgenograms, may indicate an old healed tuberculous lesion, not necessarily osteomyelitis.

Roentgenographic Features They have been presented in previous reviews. They are often only suggestive, not pathognomonic, of tuberculosis. In the early stage none may be present. Later one or more of the following features will be found (Dickson, Henderson): uniform thinning of bone cortex, destruction or thinning of articular cartilages, decalcification of bone ends, lack of new bone formation, presence of foci of bone destruction usually in epiphyses, failure of the process to extend along the shaft but a tendency to involve the neighboring joint. Bone abscesses are indicated by rarefied portions, it is not uncommon to see little notched rarefied areas on tibial or femoral margins at synovial insertions. In a knee the intercondylar notch is often enlarged. In an elbow the olecranon process may be wedged deeply between humeral condyles. In advanced stages the picture is one of destructive arthritis, which is usually more extensive than roentgenograms suggest. The incidence of the various roentgenographic features in 32 cases was noted by Taylor, Ferguson, Kasabach and Dawson. Roentgenograms in tuberculous and gonorrheal arthritis possess several features in common but the length of time required to produce changes in tuberculous arthritis is likely to be ten to twenty times as long as that required to produce corresponding changes in gonococcic arthritis.

Differential Diagnosis Early differential diagnosis is very important since only then, if ever, is cure with function possible. Diagnosis may be difficult because tuberculous arthritis may be multi-articular and atrophic arthritis occasionally may long be monoarticular. Collins and Cameron noted a case illustrating the diagnostic difficulty arising because of the following circumstances: (1) The insidious monoarticular onset of some cases of multiple, nonspecific arthritis, (2) the coexistence in the patient of some visceral tuberculous lesion which may or may not influence the course of nontuberculous polyarthritis, (3) the possible occurrence of a single tuberculous joint superimposed on nontuberculous multiple arthritis, (4) the occasional incidence of true tuberculous arthritis in two or more joints, (5) the comparative infrequency of nonspecific arthritis of a hip in patients of less than

middle age and the tendency to suppose such a condition to be tuberculous, (6) modification of the course of nonspecific arthritis due to early immobilization, (7) the possibility that there exists an atypical tuberculous form of polyarthritis—tuberculous rheumatism

Consideration of the following factors was currently stressed (Henderson, Dickson, Ghormley and Deacon) as useful in differentiation Age Tuberculous arthritis generally occurs before the age of 14 years However Dickson and Henderson not infrequently noted its appearance in patients 50 to 65 years old Family history Familial tuberculosis was present in only 8 per cent of Henderson's cases Coincident pathology Tuberculosis occurred in sites other than joints in 44 per cent of Henderson's cases, most often in lungs Precipitating factors Recent trauma, 6 to 12 weeks before onset of symptoms, followed by a prodromal quiescent period, was not uncommonly noted About 50 per cent of patients with tuberculous arthritis think they traumatized the affected joint before onset of symptoms but Henderson believes that trauma really acts as a precipitating factor in only 13 per cent of cases Appearance of joint The presence of a chronic or subacute monoarthritis should make one suspect tuberculosis The characteristic appearance is that of a boggy joint without evidence of acute inflammation, a doughy enlargement due to swollen synovia, not to hydrops Generally little or no fluid can be felt or aspirated from a tuberculous joint in contrast to the hydrops common in nonspecific arthritis Much fluid is evidence against, rather than for, tuberculosis Muscle atrophy is present, often early and extreme—out of proportion to the duration of illness Symptoms The rather late appearance of articular pain and tenderness suggests tuberculosis, in other arthritides pain is usually early and notable Course A feature of tuberculous arthritis is its indolent chronicity with periods of remission and exacerbation, the general trend is one of progression and persistence of symptoms, a residuum of symptoms remaining even in the so-called remissions

Biopsy and Guinea-Pig Tests The diagnosis of tuberculous arthritis is not easy Biopsy is sometimes necessary Pathologists are usually able to make a definite diagnosis but in doubtful cases guinea-pig tests are necessary Studying 175 cases of suspected tuberculous arthritis, W E Swift noted the relative accuracy of diagnosis made on the following clinical data, roentgenograms, frozen-sections of tissue, paraffin-sections of tissue, inoculation of guinea pigs Each method was subject to some error

Tuberculin Reaction A positive tuberculin reaction affords only presumptive evidence of tuberculous joint disease unless all other possible active tuberculous foci can be excluded A negative reaction in the absence of certain modifying factors (overwhelming tuberculous infection, advanced sepsis, anemia or other grave disease) can eliminate the diagnosis of tuberculosis with some certainty Collins and Cameron recommended Parke-Davis' Tuberculin PPD (Purified Protein-Derivative) for such tests

Treatment In 50 per cent of the 400 cases in which arthrodesis was

done at The Mayo Clinic for tuberculous spondylitis there was arrest of the disease, according to Henderson. Eradication of tuberculous bone is not possible and the operation of fusion of laminae and articulating processes posteriorly, if combined with general treatment, seems merely to hasten the process of arrest of the disease. For tuberculosis of the hip arthrodesis by combined intra-articular and extra-articular fusion was favored; results were successful in 90 per cent of 46 cases. The conservative nonsurgical treatment for tuberculous knees is preferable in children but not in adults, in the latter, surgical treatment is preferable because of the economic problem. Whether arthrodesis is to be done depends on the condition of the knee and the patient's general condition, social status, temperament, and so forth. A low grade tuberculous arthritis of a knee may exist for years with little trouble to one able to govern his activities, in such cases arthrodesis should not be insisted on. Bony fusion was successful in 89 per cent of Henderson's 248 patients with tuberculous knees, the surgical mortality was zero. For the treatment of quiescent tumor albus and tuberculous pseudoarthrosis in children Delahaye developed a completely extra-articular method of arthrodesis. In a tuberculous hip the production of solid, bony ankylosis is the best result that can be obtained, even so abscesses may develop and sinuses may continue to drain indefinitely, according to Adams.

"TUBERCULOUS RHEUMATISM"

Definition, Types Poncet (1897) described two varieties of tuberculous rheumatism or polyarthritis: an acute or subacute form and a chronic form. Basis for the diagnosis included a family history of tuberculosis and the presence in the patient of true tuberculous arthritis occurring before, with, or after the onset of the "tuberculous polyarticular rheumatism." Since Poncet, others have varied the clinical picture and extended the basis of diagnosis. According to Copeman, one variety resembles acute rheumatic fever in that joints are successively affected without permanent lesion or disability but it differs from rheumatic fever in the absence of carditis and resistance to salicylates. The second variety is that of a transitory or more chronic polyarthritis eventually becoming localized in one of the joints first affected.

Clinical Features Admittedly the clinical features of the entity have never been set forth with unmistakable clarity. Kubirschky's criteria for a diagnosis of tuberculous rheumatism were repeated^{145, 247}. Reputed clinical features are as follows (Copeman, Dickson): (1) tuberculosis often in the affected person's family, (2) visceral tuberculosis often in the affected person, (3) involvement of fewer joints than in most types of polyarthritis and a predominant involvement of one joint, (4) presence of more fever than in other forms of polyarthritis, (5) a condition refractory to salicylates, (6) absence or rarity of carditis, (7) isolation of Koch's bacillus from synovial fluid in certain cases, (8) blood cultures positive for tubercle

bacilli (Reitter-Lowenstein technic, 1934), but only during certain phases of the disease

Representative Cases Copeman found 12 cases in the literature which seemed to fulfill these criteria. Most of them were reported from France, none from England or America in 22 years. Six of the 12 cases seemed to represent an intermediate type, "not so far recorded in the English literature," in which pathologic reaction in patients' joints were atypical but injections of joint fluid produced tuberculosis in guinea-pigs.

Of the 12 patients, 10 were females, two were males. Age onset of arthritis averaged 28 years (range 17 to 66 years), three gave a history of previous attacks with increased joint damage after each the joints in the intervals being quiescent, eight noted febrile onset, four of six patients were unrelieved by salicylates, three gave a family history suggestive of tuberculosis, four previously had disease suggestive of tuberculosis, two ultimately developed frank tuberculous arthritis in one of the affected joints, all of five patients tested had positive tuberculin tests, joint fluid from eight cases and blood from one case were injected into guinea-pigs, results were "positive" for tuberculosis in six, doubtful in one, negative in two, in four cases synovial tissue at biopsy revealed "chronic inflammation", in two specimens acid-fast bacilli were seen on staining, in five cases ankylosis occurred in one or more joints.

Applying these criteria and tests to 42 of his own cases of "typical rheumatoid arthritis" Copeman detected evidence of an associated tuberculous factor in 12 cases.

(Two of these cases were abstracted in the third review—Ed.)

He concluded that a proportion (possibly 30 to 40 per cent) of all patients with true rheumatoid arthritis can be shown to suffer or have suffered from a low-grade tuberculous infection, which in certain cases at least may be related to the course of the polyarthritis, and that "tuberculous rheumatism" cannot be distinguished by clinical means from rheumatoid arthritis of other causation. Features most suggestive of the condition were the increased incidence of tuberculous antecedents (present in six of his own 12 cases), subsequent development of classical tuberculous arthritis (in two of the 12 cases), the discovery, after injection of tuberculin, of silent foci of tuberculosis (in two cases), pyrexial onset of the arthritis with marked fatigue (three of 12 cases), increased sensitivity to tuberculin in all of 12 cases, a tendency for the condition to progress by recurrent attacks with intervening quiescent periods, the isolation of tubercle bacilli from the blood (sent by Copeman to Lowenstein) of 11 of the 12 cases. Specimens of blood from 30 patients with rheumatoid arthritis in whom Copeman found no evidence of associated tuberculosis were also sent to Lowenstein, in only one case was the culture "positive for Koch's bacillus," the case of a child whose father was being hospitalized for tuberculous adenitis.

Pathogenesis, Pathology Copeman's interpretation follows. Most persons have been infected with tuberculosis in early life but have overcome the infection. In certain cases focal areas may become quiescent or slightly

reactivated but "silent" Certain cases of "rheumatoid arthritis of unknown cause" are cases of tuberculous rheumatism, the infection originating in a chronic or periodic leakage of toxic material, or of actual bacilli, possibly of attenuated virulence, from such a tuberculous focus This primary focus is of such low virulence as to cause no general symptoms but it produces in "susceptible" joints an inflammation different from classical tuberculosis The histologic appearance of synovia generally reveals "non-specific inflammation" with subendothelial collections of round cells as found in rheumatoid arthritis Perhaps the latter cells represent a halfway stage, due to altered bacterial virulence, between nonspecific and true tuberculous changes Perhaps the affected joints are sensitized by tubercle bacilli, their toxins or virus, this sensitization may be nonspecific to the extent that subsequently it can be activated by streptococci or other bacteria, not necessarily tubercle bacilli, thus presenting a "symbiotic cause" of chronic polyarthritis

Conclusion The consensus of current opinion is that this entity is not established Those who refuse to accept it base their position on the failure to find characteristic histologic changes in repeated examinations of tissue from supposed cases and the negative results of guinea-pig tests It was agreed that there seems to be no good reason why tuberculosis cannot produce a polyarthritis just as streptococci or gonococci do One cannot categorically deny the possible influence of associated visceral tuberculosis on the production and course of polyarthritis However, no definite clinical syndrome of tuberculous rheumatism has been established, no consistent experimental or laboratory evidence has been produced in support of the clinical evidence offered, and in very few of the reported cases has proof of tuberculous origin been forthcoming According to Ghormley and Deacon, "To date no proof of the tuberculous etiology of chronic proliferative arthritis exists It may be proved at a later date but this seems unlikely to us"

SYPHILITIC SYNOVITIS AND ARTHRITIS CHARCOT JOINTS

Charcot Joints The incidence of Charcot's disease in neurosyphilitic patients is not great It developed in 6 per cent of 744 tabetic patients (Moore, 1933) Epstein's patients with Charcot joints rarely present themselves because of symptoms referable to their nervous system but cause of joint disease The condition was not accompanied by any marked symptoms of tabetic disease

Pathogenesis Epstein accepted the theory of Wile and Butler (1930),—the joint changes are always associated with destruction of the afferent (proprioceptive) nerves, rendering the joint tissues insensible to trauma Under these conditions each minor injury or even physiologic trauma produces further articular pathologic lesions which accumulate to form the end picture of a Charcot joint Many restrict the use of the term "Charcot

joint" to the arthropathies of neurosyphilis. But articular disintegration similar to tabetic arthropathies may occur with syringomyelia, myelitis, poliomyelitis and gunshot wounds of the cord.

Roentgenograms Except in early cases the changes are fairly typical swelling and increased density of soft tissues, excess fluid in joints and tissues, diffuse sclerosis of bone with atrophy, erosion of joint surfaces, production of new bone, pathologic fractures, loose bodies in the joint, calcification in periarticular tissues, subluxations or dislocations (Epstein)

Cytology of Synovial Fluid Collins studied the fluid from a grossly disorganized Charcot joint of a patient who had advanced tabes. The total cell count was 250 per cu mm, with 25 per cent polymorphonuclears and 43 per cent lymphocytes.

Treatment Neurologists and syphilologists have been able to do little in these cases. Orthopedic management is more important than antisyphilitic treatment, according to Epstein, who presented eight cases in which antisyphilitic treatment alone was insufficient to check the progress of arthropathy. Conservative treatment to reduce pain and swelling and to protect the joint from trauma includes much rest, avoidance of weight-bearing, immobilization in a splint or cast if necessary, local application of heat, especially diathermy, non-weight-bearing exercises, if fluid is present, repeated aspiration to prevent undue capsular and ligamentous stretching, later suitable orthopedic supports for affected joints. Operative treatment includes correction of fractures, removal of draining sinus tracts, amputation of totally disintegrated regions such as an ankle or foot that has become "a veritable bag of bones," correction of valgus or varus position of an ankle by osteotomy, and other procedures.

Fever Therapy and Chemotherapy as Prophylaxis Since the only effective treatment of Charcot's disease is prevention it is appropriate to note that electropyrexia represents a distinct advance in the treatment of early syphilis and of neurosyphilis particularly when combined with chemotherapy (Simpson, Neymann, Lawless and Osborne). "Tabes is very favorably influenced by electropyrexia." Neymann, Bennett and Simpson noted relief from intractable root pains, gastric crises, ataxia, cord bladder, head pains, and paresthesia. Fever therapy should not be expected to affect Charcot joints.

UNDULANT (MALTA) FEVER, BRUCELLOSIS, BANG'S DISEASE

Incidence A discussion of undulant fever is appropriate because the disease commonly affects muscles and joints. Further data were presented on the increasing prevalence and recognition of the disease in the United States and in the separate states (Hardy, Jordan, and Borts), in Kentucky (Beatty), in Pennsylvania (Ervin, Hunt and Niles), in Wisconsin (Sprague), in Texas (Winans), and in the Tanganyika Territory (Wilson). Reported cases in the United States numbered 1,887 in 1934, 1,897

in 1935 The highest incidence is in Iowa, Vermont, Missouri and Kansas There were 705 new cases in Iowa According to Winans, brucellosis in office practice in Texas is more common than unsuspected syphilis Among 295 office patients studied in sequence, 10 had positive agglutination tests for undulant fever, seven gave a positive Wassermann test Discarding patients with no other signs of the disease the corrected total of cases of clinical undulant fever was 1.7 per cent of the 295 patients

Economic Importance Undulant fever is the greatest medical problem in the cattle industry Apparently 20 per cent of all cows in Texas (Green), 10 per cent of all milk goats, and 13 to 16 per cent of cows in the entire country have or have had the disease (Vreeland)

Symptoms "A disease of many forms, undulant fever in the human has no parallel, it may be latent or fulminating, acute, subacute, or chronic, local or general, febrile or afebrile, inflammatory or noninflammatory" (Green) Its symptomatology is protean and widespread and may be classical to the experienced physician but vague and mixed to the unsuspecting practitioner Textbook descriptions are inadequate and ordinarily would not lead to a diagnosis Laboratory data and the incidence of various symptoms were studied in 705 cases by Hardy, Jordan and Borts, in 300 cases by Dalrymple-Champneys, in 35 cases by Beatty, in 12 cases by Ervin, Hunt and Niles Dishongh regards the disease as without cardinal symptoms, as one "which may resemble any disease known to science" Symptoms are those of septicemia Commonest were weakness, fatigue, malaise, fever, drenching sweats, headache, "rheumatic pains" in various muscles and joints, in back, neck, chest or extremities, anorexia, constipation, chilliness or chills, epigastric, abdominal or pelvic pain, palpitation, depression, weight loss There were a host of less common symptoms Occasional complications were sinusitis, pyelitis, pleurisy, mucous colitis, seborrheic dermatitis, leg ulcers^{31, 127}

The fever is usually intermittent, remittent or undulating, but this type is not always present (Gottlieb) Secondary anemia and leukopenia with relative lymphocytosis are usually present but leukocytosis occasionally occurs²⁰⁹

Five clinical types were spoken of 1 The intermittent type, which is the commonest, is of subacute onset and there is an intermittent afternoon fever, the average duration is 1 to 4 months 2 The ambulatory type comprises 25 per cent of cases in the United States, the illness is short and mild and is featured by weakness and fever which may be high but which is quite or almost unrecognized by the patient, who may continue at work 3 The undulant type (15 per cent incidence) is marked by successive relapses, decreasing in intensity and duration 4 The malignant type (2 per cent of cases) is of sudden onset, it is an overwhelming disease of rapid, fatal termination 5 The subclinical type is unrecognized by the patient, it is asymptomatic, affects exposed persons and is discovered by the presence of agglutinins The disease presents two phases 1 The acute phase may have

an insidious or sudden onset. Prodromes are malaise and general aches, later symptoms are chill, fever, headache, backache, neckache, sweating, weight loss, acute arthralgia, abdominal pain, nausea, vomiting. 2 The chronic phase may follow the acute, or may appear independently, and is characterized by malaise, low grade fever, growing weakness, weight loss, general aches and pains. The disease is most commonly misdiagnosed as typhoid fever, influenza, paratyphoid fever.

Duration of the disease is very variable according to Beatty, who studied chronic cases, it may last four weeks to 17 years (av 37 months), according to Carpenter and Boak it generally lasts ten days to six months, occasionally six years (av three months). To determine the natural course of the disease without "specific treatment" Carpenter and Boak treated 26 patients symptomatically only, the duration was two to 72 (av 12.5) weeks.

Symptoms referable to muscles and joints. In different reports the incidence of articular symptoms was variable but generally notable. arthropathies were present in 31 per cent of Simpson's 175 cases (1930), in 32 per cent of Hardy's 375 cases which also included one case of hydrarthrosis and one of osteomyelitis. Undulant fever in Iowa has been characterized by arthritis, acute or chronic, septic or nonseptic, by spondylitis simulating Pott's disease, and by osteomyelitis (Hardy, Jordan, Borts). Wilson regarded as "very characteristic" burning pains in certain joints, especially wrists, ankles, elbows. Dalrymple-Champneys noted "arthritis and arthralgia" (no further description) in 20 of 300 cases. Four of the eight patients noted by Neumann had "rheumatic pains", one other patient had arthritis of a hip joint. Other cases of undulant fever with arthritis were noted ^{79, 147, 511, 555}. Two of Vreeland's patients had four joints severely affected, one patient, six joints. A patient of Winans had fever, pain, swelling and stiffness in ankles, wrist and spine, a negative agglutination test and blood culture but a strongly positive skin test and rapid response to appropriate treatment. Cases with arthralgia and myalgia were noted by many ^{168, 555}. Among Beatty's 28 patients, 24 had backache, 23 had neckache. According to Sprague "rheumatic manifestations," pain and swelling in joints, have been reported in about 50 per cent of cases, Vreeland often noted swollen, tender but not red joints, especially shoulders, ankles, knees, hips and sacro-iliacs.

Kulowski noted five cases of undulant fever affecting the osseous system: two cases of spondylitis, one of acute arthritis of a wrist, two of osteomyelitis (of the humerus in one instance, of skull and ribs in the other).

Case 1 Brucellosis osteomyelitis of left humerus. The patient noted insidious onset of pain and stiffness of the left arm and shoulder, which continued for four years without constitutional reactions. An abscess finally formed and was drained. Pain recurred and a deltoid sinus was incised. Brucella organisms were recovered, agglutination test was strongly positive.

Case 2 Brucellosis spondylitis. A month after "the end" of a 6½ months'

undulant fever, low back pain developed without constitutional reaction. The condition became acute and febrile. Agglutinins for *Brucella* were present—1:640 and 1:160. Spinal fusion was done.

Case 3 Brucellosis spondylitis. Low backache developed, remained insidious for seven months, then became acute. Roentgenograms showed destruction of lower lumbar interarticular facets with abscess formation. A huge prevertebral abscess was drained, *Brucella* was recovered.

Case 4 Brucellosis of wrist joint. Undulant fever developed, agglutination, 1:640. Three months later acute painful swelling affected a wrist from which pus was recovered.

Case 5 Brucellosis osteomyelitis of skull and ribs. Undulant fever developed in May. An abscess appeared over the ribs anteriorly in June, another abscess over a hip in September, other rib abscesses in October 1930. In September 1933, a skull lesion was drained, pus was sterile.

Intermittent hydrarthrosis associated with undulant fever was noted once each by Baker (1928, 1929), by Weil (1930), by Hardy and associates (1931) and by Simmons (1935). Sharpe has reported another such case.

A young man, in 1929, had painful swellings of knees, right ankle and right wrist. These persisted for 6 weeks, recurred at irregular intervals in the knees for a year. Fever was not noted. The knee swellings returned in 1933, were definitely intermittent, sufficiently painful to require repeated aspirations, and were associated with afternoon fever to 102° F. Anorexia and loss of 20 pounds had occurred. The swellings occurred in 7 to 10 day cycles, between times they disappeared completely from the left knee, incompletely from the right and were painful only at their highest level. The patient had lived on a farm, adjacent to those affected with contagious abortion, and had drunk cow's raw milk. Roentgenograms indicated "rheumatoid arthritis." Agglutination tests with *Brucella* were 1:400. Cultures of blood, urine and synovial fluid for *Brucella* were repeatedly negative. Fever and articular swellings were unrelieved by a course of Lederle's undulant fever vaccine, only partially and temporarily relieved by artificial fever therapy. Fever, hydrops and strong agglutination reactions have persisted.

(Was this really a case of undulant fever?—Ed.)

With Scott, O'Donoghue, who recently noted a septic hip due to *Brucella* (1933), reported a case of degenerative myositis from *B. melitensis*.

The patient had fever, agglutination 1:320, a positive skin reaction and was treated by goat serum and brucellin. During treatment shoulders and deltoids became painful. Within a month atrophy of supraspinatus and infraspinatus muscles and of the deltoids occurred but disappeared 10 months later. Biopsy disclosed degenerative myositis, interstitial round-cell infiltration, sterile cultures.

Diagnostic Criteria Laboratory Data A diagnosis of undulant fever depends on the presence of a characteristic or a suggestive history supported by some of the following:

1 Agglutination Tests The agglutination test is the most valuable diagnostic test after the first two weeks of the disease (Ervin, Hunt and Niles), it is most dependable in the active stage of the disease or when patients have recovered recently (Keller, Pharris and Gaub). Agglutinins against *Brucella* organisms are generally significantly present after 5 to 14

days of illness (Dalrymple-Champneys, Sprague) but it may take several weeks for tests to be definitely or strongly positive (Gottlieb) The agglutinin content of blood may change rapidly, repeated tests are often necessary before a positive test is obtained (Beatty, Dalrymple-Champneys) Titers are generally present in dilutions 1:80 or higher (Gottlieb, Sprague) but even in definite cases of brucellosis, titers may be low 1:50, 1:10, or even negative (Beatty, Sprague) Five per cent of patients never develop agglutinins (Beatty) Of 100 cases seen by Huddleson, Johnson and Bates, agglutinin titers were negative or less than 1:50 in 33 per cent Among Dalrymple-Champney's 255 cases, the average titer was 1:1500, it rose as high as 1:2500 and in only one case was it less than 1:100 Among Beatty's 35 cases the titer was 1:100 or over in 26, 1:50 in six, 1:25 in one and negative (but with positive skin tests) in two cases A negative agglutination test means either that brucellosis is absent, or that the disease is present but there is no immune response (Kemp) Agglutinins may be present for months or years after clinical recovery and titers were frequently as high as 1:640 after 4½ years (Dalrymple-Champneys) (Meanwhile an unrelated atrophic arthritis could develop Therefore every polyarthritis with positive agglutinins for *Brucella* must not be attributed to brucellosis—Ed) After clinical recovery titers usually fall rapidly, a continued high titer suggests latent activity Donham and Fitch developed a modified technic to discover agglutination earlier

2 *Precipitin Tests* Sera from patients with positive agglutination reactions also gave positive precipitin reactions with one or more polysaccharides but Higginbotham and Heathman consider the precipitin tests less practical than agglutination tests

3 *Complement-Fixation Tests* Although Thomsen (1931) found these positive oftener than agglutination tests, others^{200, 262} found them more difficult and not as reliable as agglutination or precipitin tests

4 *Intradermal Test* The technic and interpretation of this test were again described^{81, 127, 298, 581} *Brucella abortus* antigen is used Tests become positive after 7 to 11 days of disease (Sprague) A positive test is especially helpful for diagnosis in active cases when agglutination tests are negative (Ervin, Hunt and Niles) A diagnosis should not be made only on the basis of a positive skin test 20 per cent of residents in certain communities give positive tests (Carpenter and Boak) Tests were positive in 5 per cent of one group of 576 persons, living or working under conditions favorable to *Brucella* infection (Keller, Pharris, and Gaub) Kemp considered them more reliable than tuberculin tests in tuberculosis, a positive test may be incidental to a given diagnostic problem as it indicates previous as well as active infection (Gottlieb)

(The antigen is irritating Controls should always be tested simultaneously with suspects—Ed)

When it is desired to study both agglutination and intradermal tests,

agglutination tests should be done first because injections of the amount of material used for skin tests will of themselves promote agglutination reactions in titers of 1 50 to 1 200, thereby providing a source of error (Winans)

5 *Cultures* The organism may be isolated by special technic^{127, 579} from blood, urine, feces and other sources. Cultures of blood are more successful than those from other material, even so they are often negative, difficult to make, and less often used for diagnosis than other tests^{208, 511}. However, much can be learned therefrom regarding types of strains and they should be made oftener²³⁶. They usually become positive 3 to 15 days after the patient's inoculation⁵⁵⁵. They were positive in 16 of 85 cases (Huddleson and associates). Poston and Smith recovered *Brucella* from spinal fluid by a new technic whereby the germs can be grown after being precipitated by specific agglutinating serum.

6 *Guinea-Pig Inoculations* These are unsatisfactory as the test requires 4 to 6 weeks' observation and lesions resemble tuberculosis (Kemp).

7 *Opsonophagocytic Activity of Blood* This test was originated by Huddleson, Johnson and Hamann (1933), its value in determining a patient's immunity was confirmed by Keller and associates, who discussed technic and interpretation. With it, in conjunction with the skin test, one can determine which patients are susceptible, infected, or immune to undulant fever.

A low phagocytic activity and a negative skin test indicate susceptibility to brucellosis. A low or negative phagocytic activity with a positive skin test indicate infection without immunity. Marked phagocytic activity indicates developing or established immunity. Marked phagocytic activity and a positive skin test indicate that fever in a given case is due to some disease other than undulant fever.

8 "*Therapeutic Test*" Most of Beatty's patients with undoubted brucellosis noted accentuation of symptoms, malaise, general aching, as a reaction to intramuscular injections of undulant fever vaccine. Beatty considered this reaction of diagnostic significance.

TREATMENT OF UNDULANT FEVER

After reviewing 67 reports Carpenter and Boak regarded the efficacy of specific therapy unproved. The disease is self-limiting, subject to spontaneous remission or cure. They found no definite evidence that "specific therapy" shortened the disease, symptoms lasted an average of 12.5 weeks in those treated "specifically," 11.3 weeks in those treated symptomatically. General measures for the disease were again stated^{127, 581}.

Chemotherapy, Intravenous Antiseptics Various chemicals, arsenicals, dyes, acriflavine, and so forth, produced no beneficial effect unless a febrile reaction was induced^{31, 79, 299}.

Specific Vaccine Twenty-seven reports noted results in 350 patients treated with stock or autogenous vaccines. Results obtained had little to do

with the type of vaccine used but depended on the production of systemic reactions⁷⁹ Among 21 other patients only four were benefited by stock vaccine, only one of six benefited by autogenous vaccine (Dalrymple-Champneys) It was considered "beneficial" by Dishongh, "helpful but not curative" by Winans, "fairly satisfactory" by Beatty all of whose 23 patients were improved, some markedly, others slightly

Toxic Filtrates These produced no effect unless "shock" was induced (Carpenter and Boak)

Brucellin This seemed useful to some²⁷⁵, in 100 cases the average illness before treatment was 159 days, after treatment, 18 days

Antiserum Results with convalescent and animal sera noted in 13 reports were generally favorable, not spectacular (Carpenter and Boak) Superior to his older serum is Foshay's new antibrucellosis (horse) serum which is definitely antitoxic according to Bannick and Magath Poston and Smith treated two patients successfully with intrathecal injections of human immune serum Two patients were successfully treated with immunotransfusions by Creswell and Wallace who used the opsonophagocytic index in selecting donors

Foreign Protein Therapy Wilson, and Carpenter and Boak occasionally noted rapid recovery and excellent results from the shock and fever reactions of T A B (triple typhoid) vaccine Results in 12 cases of Ervin, Hunt and Niles were "uniformly successful" because of febrile reactions which presumably stimulated specific or nonspecific immunity After three to six doses of the vaccine, symptoms cleared and agglutination tests became negative Nine of the 13 other patients were also definitely helped thereby (Dalrymple-Champneys)

Fever Therapy Carpenter and Boak treated three patients with artificial fever two were promptly cured, one patient's symptoms, including arthritis, were stopped but a year later "the specific arthritis" returned Recalling the good result noted by Simmons (1935) who treated by means of artificial fever a case in which the disease was associated with severe hydrarthrosis, Prickman and Popp treated four patients without arthritis Prompt results were obtained with three fever sessions, each for five hours at 105 to 107° F Curiously the natural fever continued until the last fever session, then stopped rather abruptly, not before *Brucella abortus* in vitro can survive 24 hours at 107° F⁵⁴⁵ Therefore fever therapy alone probably does not kill the bacteria in vivo, corollary cytologic and immunologic reactions are stimulated

Fouadin (Antimony Bis-Pyrocatechin Disodium Sulphonate) This substance injected intragluteally benefited eight of Neumann's patients

Criteria of Cure, Mortality Angle's (1935) criteria of cure were (1) disappearance of subjective symptoms, (2) increasing weight, (3) gradual disappearance of fever, (4) lowering of agglutinin titer, (5) return of normal blood picture, (6) subsidence of neurologic symptoms The reported mortality is 1 to 4 per cent, in severe outbreaks, however, it may be as high as

13 per cent^{511, 555} Death in one series resulted in two of 100 cases²⁷⁵, in nine of 290 other cases,¹²⁷ in one of 26 patients,⁷⁹ and one of 35 cases³¹ Gottlieb's patient at death exhibited usual features, splenitis, lymphadenitis also, rare features subdiaphragmatic and hepatic abscesses

Prophylaxis This can be accomplished by using only boiled or pasteurized milk, and by inspection of herds—the use of blood tests for all cows and goats and the segregation, or preferably destruction, of affected animals^{31, 211}

TYPHOIDAL SPONDYLITIS “TYPHOID SPINE”

Cases of typhoid fever, especially “typhoid spine,” are now rare in the United States A few members of the Civilian Conservation Corps recently developed typhoid fever in Texas, one developed “typhoid spine” (Bowen and McGehee)

Positive blood cultures proved the diagnosis of typhoid fever in a boy, aged 15 years After desperate illness for two months he convalesced one month, then developed dorsal scoliosis, lumbar pain and rigidity Roentgenograms showed typhoid spondylitis in various stages Treatment included immobilization of the spine on a Bradford frame, later a brace was worn for six months

Typhoid spondylitis may occur during the fever or during convalescence It produces paroxysmal attacks of intense pain, tenderness, and muscle spasm, generally lumbar Roentgenograms show localized areas of rarefaction near corners of vertebral bodies, thinning of disks, subsequently the development of a heavy bony bridge about the focus and disk Suppuration has not been noted

Campbell and Greenfield found post-typhoid suppurative osteitis in a case previously called “rheumatism”

In 1922 the patient, a young man, had typhoid fever Long afterward he was still a typhoid carrier Ten years later, without intervening illness, he developed a painful left arm, diagnosed “rheumatism” Pain recurred the next year without fever, rose spots, splenomegaly or other features of typhoid fever A bone abscess in a humerus was drained, a pure culture of *Bacillus typhosus* was obtained therefrom The agglutinin titer was 1:250

MENINGOCOCCIC ARTHRITIS

Joints are involved in 4 to 7 per cent of cases of meningococcic meningitis²⁴⁶ A case of meningococcal suppurative arthritis of cryptogenic origin was reported by Campbell and Greenfield

A colored infant, aged 15 months, developed an inflamed knee joint with fever of 103° F Pus was removed therefrom, the child improved immediately Cultures of pus revealed *Neisseria intracellularis* which agglutinated with polyvalent meningococcus agglutinating serum up to a titer of 1:100 of the serum The patient did not have meningitis

Fever Therapy for Meningococcic Infections Sustained artificial fever at 107° F is effective against certain strains of meningococci Thermal deathtime studies by Bennett, Person and Simmons showed that most strains died out on a water bath at 106.8° F, within eight hours Two cases of proved chronic meningococcic infections (neither with arthritis), were cured by artificial fever Artificial fever therapy will probably not replace serum therapy, because of the danger of severe cerebral edema and medullary failure fever therapy is probably contraindicated in acute meningitis It may have a place as adjuvant therapy in subacute or chronic meningococcic infections unrelieved by serum or in meningococcemia

PYO-ARTHRITIS PURULENT (SEPTIC) ARTHRITIS

Acute septic arthritis arises in three ways Bacteria reach the joint (1) By direct introduction into joints from penetrating wounds, knees are thus affected most often but this is the least common type of septic arthritis in civil life, (2) by direct extension of para-articular infection, most commonly osteomyelitis, into a joint, (3) by the blood stream from distant foci of infection This type, "metastatic arthritis," is the most frequent and may follow measles, scarlet fever, gonorrhea, pneumonia, meningitis, subacute bacterial endocarditis, in association with any septicemia, for example, from abscesses in tonsils, teeth, or prostate, from boils or infected skin, from scratches or wounds Of seven cases of septic arthritis of hips in children seen by Freiberg and Perlman, six originated from otitis media or mastoiditis, one from trauma, one from unknown source Of 16 cases affecting knees seen by Eggers, seven originated from puncture wounds or other trauma, one from pharyngitis, three from pneumonia, one from osteomyelitis, four from other causes Regan's four cases in hips arose from cystitis, sinusitis, oral infection, tonsillitis

Invading bacteria are generally *Staphylococcus aureus* or hemolytic streptococci, less commonly other streptococci, gonococci, pneumococci, meningococci, typhoid bacilli, influenza bacilli (Harris) In current series organisms recovered were staphylococci, hemolytic and nonhemolytic streptococci and pneumococci (Eggers, Freiberg and Perlman, Regan)

Clinical findings as currently reviewed are usually definite abrupt onset of pain, redness and swelling of a joint, often after trauma, capsular distention, muscle spasm in flexed position, marked constitutional reactions, fever, leukocytosis, sometimes positive blood cultures Aspiration of the joint reveals pus and confirms the diagnosis Badgley and his colleagues reported 113 cases of septic hips

Pathology Depending on the severity of infection, pathologic reactions vary from mild synovitis to a devastating articular infection that may end in death They were briefly summarized in recent articles^{9, 194, 195, 238} Most important are changes in cartilage which, once destroyed, is not replaced Variable degrees of destruction occur, not by the direct action of bacteria

but by the action of proteolytic enzymes in the leukocytes of pus, to a lesser extent by pressure and by synovial pannus. The microscopic appearance is the same in various pyo-arthroses irrespective of the invading bacteria.

Roentgenograms In the early stage roentgenograms show little or nothing in the hematogenous type of septic joints. In other types they may reveal penetrating wounds or osteomyelitic foci^{9, 238}. Later, variable degrees of destructive arthritis are seen but then roentgenograms are of no diagnostic, only of prognostic, help.

Differential Diagnosis Differentiation must be made from rheumatic fever, gonorrheal arthritis (which may also produce septic joints), juxta-articular osteomyelitis without secondary arthritis, less often hemophilic arthritis^{9, 238}. In osteomyelitis of juxta-articular bone, maximal tenderness, swelling and pain are over the epiphyseal line rather than the joint. If the joint is still not secondarily affected it moves without pain through a partial range of movement. The most valuable clinical symptom in differentiating acute septic arthritis from periarticular lesions is that the patients with septic arthritis often have severe pain on the slightest degree of passive motion, induced even when adjacent muscles are completely relaxed (Armstrong).

Diagnosis is easy when classical symptoms are present: initiating trauma or infection, fever, leukocytosis, one swollen painful joint, generally in a child. All writers emphatically urged that in case of doubt diagnostic aspirations, repeated if necessary, are urgently indicated. "Their value cannot be overemphasized." By aiding early diagnosis they provide the only sure means of protecting the joint, which will be seriously damaged or perhaps completely destroyed if diagnosis is delayed^{9, 160, 238}. According to Armstrong, "monarticular lesions should always be considered septic until proved otherwise."

(We agree that *acute* monarthritis with marked *constitutional reactions* should always be regarded as septic arthritis until proved otherwise. Commonest forms of acute monarthritis (much commoner than septic arthritis) are traumatic arthritis, nonseptic gonorrheal arthritis or gouty arthritis. In acute gouty arthritis the local pain and inflammation may be intense but constitutional reaction is usually mild.—Ed.)

When a wound occurs in the vicinity of a joint it is sometimes difficult to determine whether or not it has entered the joint. Harris' procedure is to insert a needle into the joint distant from the wound and inject a small amount of ether, if the wound penetrated the joint ether will boil out of the wound.

Complications of Septic Arthritis The following complications were noted by Badgley and his colleagues among 113 cases of septic hips: disappearance of the femoral head in 43 cases, sequestration of femoral head in 21 cases, epiphysiolysis in nine cases, dislocation of the femoral head in 34 cases, nearthrosis at the epiphyseal line with fusion of head to acetabulum or ilium in eight cases, coxa magnum in 5 cases. Freiberg and Perlman observed seven cases in which inguinal lymphadenitis and iliac abscesses

were secondary to septic hips "No similar cases have been reported previously" The question was raised Are secondary iliac abscesses unrecognized but common complications of septic hips? Hepler noted five cases of septic hips from pelvic osteomyelitis in which the bladder became markedly displaced by intrusion into the pelvis of an enormous involucre to which the bladder became attached and was displaced laterally In such cases perforation of the bladder by sequestra and production of osteovesical fistulas threaten or impend When perforation occurs, as it did in two cases, it is chronic or subacute, with the entire side of the bladder firmly adherent to the involucre so that there is no urinary extravasation or leakage, and no signs or symptoms referable to the urinary tract Therefore cystograms should be made routinely, as the condition occurred in every child with chronic suppurative arthritis of the hip and pelvic osteomyelitis which Hepler saw in the last six years

(One of us, J A K, believes these cases are very unusual and that such routine cystograms are not advisable—Ed)

Treatment Regan gave a brief historical résumé of treatment from the alpha of amputation to the omega of ankylosis Of supreme importance are early diagnosis and early *adequate* drainage Repeated aspirations, drainage through small incisions, or aspiration with injection of antiseptics are usually inadequate in severe cases Cases "cured" thereby are probably mild ones which would have recovered without surgical interference^{160, 238} Favorite methods of surgical drainage were described^{9, 15, 100, 194, 238, 449}

Patients are extremely toxic, transfusions, dietary care, relief from severe pain by narcotics are necessary¹⁶⁰

Prognosis, Results of Treatment Prognosis is generally grave Several factors determine the end result, results are better in the young than in those with joints traumatized by wear and age Results are less satisfactory in hips (Regan) than in certain other joints Some⁴⁴⁹ say that results depend to a marked extent on the type of infection, that staphylococci produce ankyloses earlier and oftener than streptococci, others say just the opposite The primary site of infection, not the germ, is the chief determining factor The presence or absence of primary juxta-articular bone disease is the important factor in persistency of trouble^{15, 160}

Of equal or greater importance is the promptness with which the diagnosis is made and drainage instituted, for this determines the degree of damage to cartilage from proteolytic enzymes in pus^{9, 238} The only good results obtained by Regan occurred when treatment was instituted within the first six days of disease Of Egger's patients, seven recovered some function, six developed ankylosis, two had amputations, one died of empyema Of patients of Freiberg and Perlman, one retained good hip motion, three developed marked limitation, three ankylosis Of the 113 patients of Badgley and associates seven retained normal function, 23 regained 50 per cent normal function, 83 developed irreparable articular damage with

numerous complications, of the latter 12 died of septicemia, two of post-operative complications

Experimental Embolic Staphylococcus Arthritis Kistler gave rabbits intravenous injections of (1) fully virulent, (2) partially sterilized, and (3) killed agglutinated and nonagglutinated saline suspensions of *Staphylococcus aureus*. Of the surviving animals that received living organisms, 100 per cent developed marked exudative arthritis with cartilaginous and osseous destruction, 53 per cent, endocarditis and suppurative pericarditis. Agglutinated and partly or almost completely sterile organisms produced even more marked and more chronic suppurative articular and subchondral lesions. Suspensions of completely sterile bacteria, whether agglutinated or not, produced no significant lesions.

RHEUMATIC FEVER

Incidence Factors which govern the incidence of this disease pertain to geography and climate, season, economic factors, age and sex.

Factor of Geography and Climate Nichol again summarized available data on the hospital incidence of rheumatic fever and of rheumatic carditis in various parts of the United States, from latitude 47° N (Spokane) to latitude 25° N (Miami). The data revealed a definite inequality in the distribution of the disease, the incidence being much less in the southern states. In West Virginia the acute stages of the disease are likely to be mild or absent but subsequent rheumatic carditis is common.⁵¹⁹

In Nebraska the disease is common.⁵⁴⁴ Christie noted that although the general incidence of rheumatic carditis was low, the hospital incidence among children in the San Francisco and University of California Hospitals was double or triple that of similar hospitals elsewhere in the country. This incidence cannot be blamed on the numerous health-immigrants to California since the incidence of rheumatic carditis is low in Los Angeles. Perhaps in northern California after an apparently typical onset and course the disease becomes "benign" and is not recognized in school examinations. In Wichita Falls, northern Texas, Whiting found the incidence of rheumatic fever and chorea to be $\frac{1}{8}$ that of Virginia, $\frac{1}{14}$ that of Boston.

(Since rheumatic carditis is more prevalent among those of lower economic strata may not his failure to include negroes have resulted in an artificially low incidence? —Ed.)

Physicians in the Mississippi Valley see about $\frac{1}{6}$ as much rheumatic fever as those in New York, according to Kinsella.

Each year from 15,000 to 30,000 deaths from rheumatic carditis occur in England and Wales, 1500 in Ireland.^{371, 393} In England and Wales 1 per cent of students entering, and 2.5 to 3 per cent of those leaving, urban elementary schools have rheumatic carditis and 1500 children under the age of 15 die therefrom each year.³⁷¹ In Ireland the incidence of rheumatic

fever varies from 1.03 per 1000 rural school population to 7.72 per 1000 urban school population. Statistics were presented on the incidence of juvenile rheumatic carditis in various cities of the British Isles^{393, 455}. Carditis was five times as prevalent as tuberculosis in Glasgow and Edinburgh schools. One-third of all London children who were chronic invalids were crippled by rheumatism in some form.

Rheumatic carditis can no longer be considered a rare disease in India. According to Banerjea's statistics rheumatic fever is almost as common in South India and Bengal as in England and the United States. It is common also in the Bombay Deccan although not as prevalent as in other countries, of 100 cardiac cases in Miraj, 47 were rheumatic (Carruthers). Thus the percentage of heart disease of rheumatic origin was actually greater than elsewhere but the carditis tended to be less severe. Kar also noted the disease in India.

Seasonal Incidence The disease was most prevalent in San Francisco in the first four months of the year⁸⁵, in Minneapolis, in early spring and late fall⁴⁸².

Social and Hygienic Factors Most of the rheumatic children seen by Ash came from poor families. Eighty-three per cent were white, 17 per cent were negroes. The relative insusceptibility of negro children suggested that malnutrition and poverty are not sole contributing factors.

Hereditary and Familial Factor Among 370 children studied by Shapiro were 201 with rheumatic carditis, 169 with nonrheumatic cardiac disorders. The incidence of rheumatic fever was three times as great in the families of the rheumatic group as in those of the nonrheumatic group.

Others noted a familial incidence of 32 per cent,⁸⁵ 24 per cent²² and 18 per cent¹⁹⁷.

Factor of Age The disease may begin at any age but further statistics again indicated that it generally begins in persons before the age of 10, especially between five and seven years^{11, 22, 80, 85, 197, 307, 455, 482, 568b}.

Factor of Sex In the new American series the sex incidence as usual was slightly greater among females, the incidence in females being from 52 to 59 per cent^{11, 85, 197}. Rheumatic chorea was much more common in females, Ash's ratio being 1 choreic boy : 2.5 girls.

The sex incidence was strongly reversed in the two series of cases from India. Seventy-seven per cent of Carruther's cases and 88 per cent of Banerjea's cases were in males. This may be due to the fact that especially in India women are more apt to be treated at home. Banerjea could not accept this idea because the relative preponderance of the disease in males prevailed in his private practice also.

GENERAL SYMPTOMATOLOGY AND PATHOLOGY OF RHEUMATIC FEVER

Swift's definition of rheumatic fever¹³⁸ affords a basis of understanding of its protean symptomatology. "Rheumatic fever is a disease of undeter-

mined etiology characterized by fever and a toxic state, and by the presence in certain organs of the body of small, disseminated focal lesions of a proliferative type. In acute stages there is also an exudation in and about the joints and sometimes in the pleura and pericardium. The term "acute rheumatic fever" has been widely objected to, in 1928 the American Heart Association dropped the use of the adjective "acute."

Clinical Phases and Types According to Coburn and others there are three clinical phases in the development of an attack: (1) an acute upper respiratory infection lasting a few days, (2) the "silent phase" immediately thereafter with no clinical symptoms and signs—it lasts for a few days to six weeks, generally one or two weeks, (3) the attack phase—the period of rheumatic manifestations varying widely in intensity and duration. Subsequently the disease runs any one of three courses: monocyclic, polycyclic or continuous.¹³⁸

Histopathologic Reaction Underlying Symptoms Swift and Derick again described the two basic inflammatory reactions, knowledge of which is so helpful in understanding the symptoms and pathology of the disease.

Two different pathologic reactions occur, exudation and proliferation, both are tissue responses to injury. An exudative reaction provides, for example, the acutely swollen joint, the proliferative reaction produces subcutaneous nodules and the myocardial Aschoff body. The two reactions are not mutually exclusive, often they coexist. The exudate consists of plasma or of synovial fluid and wandering cells, this reaction is earlier and more evanescent than the proliferative reaction. The latter appears later and is more lasting. Cells comprising the proliferative reaction are apparently not phagocytes, nor are they the epithelioid cells seen in tuberculosis or syphilis. Primitive cells, they arise from resting mesenchymal cells or from endothelial elements. Their peculiar arrangement as submiliary nodules is specific for the disease, according to some, nonspecific according to others.⁵³²

Klinge (1933) recently emphasized another feature which he believes precedes and is responsible for the proliferative tissue reaction, namely, an alteration in the intercellular mesenchymal substance demonstrated by evidences of injury to collagen fibers varying from simple focal edema to fibrinoid swelling and focal necrosis. The cause of the fibrinoid swelling is unknown. Such changes can be induced by bacteria or bacterial toxins but not by viruses. Fibrinoid swelling is also present in experimental scurvy. Thus, it is not a specific reaction. It may be a manifestation of tissue hyperergy, Klinge noted it in tissues of rabbits repeatedly injected with foreign protein.

SPECIAL CLINICO-PATHOLOGIC DATA CONCERNING RHEUMATIC FEVER

Incidence of Various Symptoms In Ash's 416 cases the initial symptom was febrile polyarthritis in 58 per cent, chorea in 21 per cent, carditis in 17 per cent. In Christie's 116 cases the initial symptom was arthritis in 68 per cent, chorea in 28 per cent, carditis in 21 per cent, tonsillitis in 19 per cent, nodules in 10 per cent, other symptoms less frequently. Among the 73

cases of Gibson and Denenholz the initial symptom was arthritis in 57 per cent, carditis in 35 per cent, chorea in 8 per cent. In adults, polyarthritis is a more common feature than carditis but in children the reverse is true a child may have only one or no joints affected (Derick)

Joints Articular symptoms were present some time during the disease in from 58 to 76 per cent of new cases reported^{11, 85, 197} including those from India^{22, 80}. Rarely the arthritis of rheumatic fever may be so persistent and marked as to simulate acute arthritis deformans⁵³². Generally articular symptoms were transient, chronic arthritis was practically never produced. "Rheumatic fever always discards its articular features eventually" (Kinsella)

Most "growing pains" and leg aches in children are not rheumatic, according to Shapiro who again differentiated between the rheumatic and non-rheumatic variety^{247, 482}.

Heart Statistics on the incidence and type of cardiac disease in the current cases conformed to previous data^{11, 85, 197, 307, 482, 572, 577}. Although the heart is practically always affected, the cardiac damage does not persist in all cases and Derick often noted disappearance of disturbances of conduction time. "The heart is frequently spared in the first attack, rarely in the second, probably never thereafter". Of Banerjea's patients in India 12 per cent had "active carditis," 60 per cent had mitral stenosis, 8 per cent had aortic insufficiency, 12 per cent had mitral stenosis and insufficiency, and in one case (4 per cent) mitral and aortic stenosis and aortic insufficiency were present. According to Carruthers, multiple valvulitis is distinctly less common in India than in the United States. But the percentage of cases of rheumatic carditis with no previous history of rheumatic fever was no greater in the Bombay Deccan than elsewhere. Therefore Carruthers could not agree with McLean (1932) that there is a greater incidence of rheumatic carditis without rheumatic fever in the South.

Some cardiologists state that organic mitral regurgitation is rare and never causes serious disability, and that high grades of mitral disease always involve mitral stenosis. However, according to Dana and Reidy pure mitral regurgitation is not uncommon, occurs in 20 to 50 per cent of all cases of rheumatic mitral valvulitis, and it alone can cause death, uncomplicated by disease of other valves or by pericarditis. Pure mitral stenosis is rarely found at necropsy and its clinical importance is much overemphasized. Contrary to the belief of some, rheumatic fever does not predispose to arteriosclerotic coronary disease in later life, according to Gross and Oppenheimer.

Acute rheumatic myocarditis is one of the rare causes of sudden death. Not preceded by a history of rheumatic fever or carditis, it caused the sudden death of a 59 year old woman in whose heart Mallory found more Aschoff bodies per cu mm than he had ever seen before. Studies on the pathology of valves, valve rings and the auriculoventricular conduction system in rheumatic fever were reported^{196, 215, 216, 217}.

Pericardium Clinical signs of acute pericarditis were noted in 12 per cent of cases,^{11, 80} 14 per cent⁴⁵⁰ and 19 per cent¹³⁸ Other data on rheumatic pericarditis were reported^{188, 117} Rheumatic fever rarely causes significant pericardial effusions, "only an examination candidate revels in paracentesis pericardii" ^{107, 438, 439}

Lungs Rheumatic pneumonia occurred in 7.6 per cent of Ash's 416 rheumatic children, appearing only in those severely affected Bronchopneumonia or lobar pneumonia may occur at any stage of the disease, according to Willius Poynton listed four types of pulmonary complications 1 Massive collapse may occur, usually on the left, sometimes on both sides It is early manifested by intense tubular breathing at the lower angle of the scapula, which then spreads downward When classic it has no other adventitious signs and will appear, disappear, reappear and disappear 2 Bronchopneumonia may appear alone or may complicate massive collapse 3 Pleural effusion may appear and necessitate paracentesis 4 Acute edema of lungs—sharp, bright crepitations commencing in upper lobes—was noted by Poynton only in patients receiving large doses of salicylates Mallory stated, "So far I have no clear conception as to whether there is a rheumatic pneumonia entity I cannot make head or tail of the descriptions" Noted by him were multiple focal areas of hemorrhage through one lung, looking much like infarcts but usually not leading to complete necrosis of lung tissue, also microscopic lesions were seen in some of the very small pulmonary arteries near hemorrhagic foci Histologically the lesions were "about half-way between infarcts and pneumonia in appearance"

Chorea (as a Symptom) Chorea was noted in 5 to 34 per cent of current American cases^{11, 85, 197, 572} but in very few of those seen in India^{22, 80}

Nodules Subcutaneous nodules were noted in 2.4 per cent of Ash's cases, in 8 per cent of Banerjee's cases, but in 37 per cent of the fatal cases of Gibson and Denenholz Not all "fibrous nodules" are actually fibrous some can appear and disappear within three days Rheumatic nodules have three zones an outer one of swollen fibrous tissue containing distended capillaries, a middle one full of leukocytes and mononuclear cells and a central zone of necrosis (Poynton)

Abdominal Symptoms Writers are stressing the fact that abdominal pains may be one of the rheumatic symptoms They occurred in 13 per cent of Ash's 416 cases, in three cases symptoms warranted surgical operation, only acute generalized mesenteric lymphadenitis was found (However in three others intercurrent acute appendicitis was found at operation) Wolffe and Brim reviewed the literature thereon, reported three such cases, and summarized the features of these and other cases

The gastrointestinal inflammation produces recurring spells of abdominal cramps Attacks may be acute or chronic When acute, the cramps may last a few minutes or a few hours The pains are sharp, sometimes about the umbilicus, sometimes generalized, but usually epigastric and not radiating Nausea may be present, occasionally vomiting Abdominal tenderness may or may not be present, rigidity

is absent. An episode is usually over before the next meal and the child generally continues to eat and play. Constipation is generally present, also slight fever, rarely over 101° F. There may be a history of slight nose bleeds or of pains in muscles and joints, or the cramps may be the only subjective rheumatic manifestation. Attacks may recur over a period of six months to several years. If the condition is chronic the patient notes mild attacks of fleeting abdominal pain from time to time without other signs or symptoms except occasionally diarrhea alternating with constipation. Unlike appendicitis, successive attacks become milder.

Laboratory Data (Electrocardiograms, Sedimentation Rates, Blood Counts, Urinary Studies) The practical value of the electrocardiographic Lead IV is "definitely limited" according to Robinow, Katz and Bohning who studied results in normals, in children and in adults with active and inactive rheumatic fever.

Erythrocyte Sedimentation Rate The close relationship between rheumatic activity and altered sedimentation rates received further notice. The test allows accurate observations on the progress of the disease but other conditions which alter the test must be known. According to Payne and Schlesinger the rate is not altered by an uncomplicated common cold or by "chronic" tonsillar infection but is notably altered by acute tonsillitis and influenza. In acute chorea there is no, or only a small, transient, increase of rate. Congestive cardiac failure has a curious effect on the rate, however active the rheumatic process may be, the onset of congestive failure and edema causes the rate to fall from a previous high figure, sometimes to normal. Such a fall in the presence of active disease is a bad prognostic sign. When nodules are present the test has prognostic significance, a fall of the rate heralds their disappearance. "Miniature rheumatic fever" is characterized by slight fever and transient tachycardia. Such a state, precipitated by tonsillitis or respiratory infection, may be subclinical but is indicated by changes in the rate.

To determine the mechanism of production of increased rates Coburn and Kapp studied changes in rate occurring in the three phases of a rheumatic attack: the pharyngitis or respiratory infection, the silent phase, and the phase of attack. In rheumatic patients who did not develop an exacerbation after pharyngitis, sedimentation rates were either not or very slightly and briefly (for 10 to 15 days) altered, but in those in whom pharyngitis precipitated a rheumatic exacerbation the rate suddenly rose to a high level late in the "silent" phase just before "the attack." By varying the concentrations of plasma protein Coburn and Kapp determined that increased rates in acute rheumatism are caused by an increase in plasma fibrinogen and globulin.

Removal of total serum lipoids and crystalloids did not appreciably affect the rate. Dilution of plasma with Ringer's solution slowed the rate as did removal of fibrinogen. Removal of globulin and fibrinogen inhibited rates almost completely. Adding globulin, but especially fibrinogen, increased the rates. The globulin and fibrinogen in blood of rheumatic patients was qualitatively the same as that in normal blood. It was suggested that fibrinogen and globulin are produced by the reticulo-endothelial system.

Blood Counts The behavior of eosinophilic polymorphonuclear leukocytes in rheumatic fever is similar to that seen in other infections. Friedman and Holtz noted that eosinophiles are absent or diminished in number during the height of acute rheumatic polyarthritis and carditis, and reappear during the stage of recovery, so that there is a postinfectious eosinophilia as in other infections. Long continued aneosinophilia and hypo-eosinophilia during acute polyarthritis or during acute or chronic carditis indicate intensely active infection. Recurrent and continuous eosinophilia indicates convalescence.

The sedimentation rate is a more sensitive and practical index of rheumatic activity or inactivity than the Schilling count (Struthers and Bacal, Rogatz). In the acute stage there is a marked shift to the left in the Schilling hemogram, that is, the percentage of immature polymorphonuclear leukocytes rises above 10. As the disease becomes inactive the shift returns to normal with, or often two or more weeks before, the sedimentation rate. Patients should not be allowed up until the sedimentation rate is normal.

Synovial Cytology Sterile fluid from a synovial effusion of one febrile rheumatic patient contained 7200 total cells per cu mm with 92 per cent polymorphonuclears.⁹³

Urine Coproporphyrin in abnormal amounts was found by Kapp and Coburn in the urine of patients with acute rheumatic fever, concurrently with onset of symptoms. Normal amounts were found in the urine of patients with inactive rheumatism. Its appearance bore no relationship to fever, hematuria or therapy, and probably indicated some kind of hepatic damage.

RELATIONSHIP OF RHEUMATIC FEVER TO OTHER DISEASES

To Subacute Bacterial Endocarditis Reports under review contained no new comments on this point. Death from subacute bacterial endocarditis occurred in a few cases.^{455, 482, 572}

To Atrophic Arthritis Most physicians believe that rheumatic fever and atrophic arthritis are not manifestations of the same disease and bear little or no relationship to each other.^{8, 271} In the United States acute atrophic arthritis practically always leaves persistent articular damage, rheumatic fever "always discards its articular features."³⁰⁷ Although Cecil did not regard the two as the same disease he thought they might be related etiologically. Dawson and Tyson considered them closely related, differing in degree rather than in kind. According to them rheumatic fever and atrophic arthritis tend to occur in the same families. Each disease appeared with almost equal frequency (14 and 15 per cent respectively) in the families of 100 patients with atrophic arthritis. They considered the geographic, age and seasonal incidence and the precipitating factors, to be about the same in both. Subcutaneous nodules of "very similar nature" appear in both.

(We do not believe they are similar—Ed.)

However, immunologic differences obtain in rheumatic fever anti-streptolysins are high, streptococcal agglutinins are not, in atrophic arthritis the reverse occurs. Even so hemolytic streptococci may play a rôle in both diseases. But even were both caused by the same agent they could be different diseases, witness the relationship between syphilis and yaws. Although the two diseases may represent different responses to the same or closely related agents, Dawson and Tyson stressed the importance of differentiating them clinically, for each has its own symptoms, therapy and prognosis.

(Too much credence cannot be given statements that both diseases are rare in the tropics. Statistics published elsewhere²⁴⁷ and herein tend to refute this idea. If the differences between the two diseases depend largely on age, one should not so frequently see Still's disease (juvenile atrophic arthritis) in children or an initial attack of classical rheumatic fever in adults more than 40 or 50 years of age—Ed.)

Differential Diagnosis Kinsella and Archer reviewed the usual points which differentiate the disease from Still's disease, acute atrophic arthritis, gonorrheal arthritis and gout. Annually there are reported one or two cases of leukemia simulating acute rheumatism, presenting fever and joint pains. Conybeare reported such a case.

Course and Prognosis "As the heart goes so goes the disease" is a timely but truthful paraphrase. The principal cause of heart failure is not physical strain but continued infection, in particular the prolonged activity of the rheumatic infection, according to Werner. Respiratory infections lowered the cardiac reserve of 50 per cent of Werner's patients with rheumatic carditis but also of the same percentage of those with syphilitic carditis. The rôle of respiratory infections therefore seemed to be nonspecific.

Effect of Pregnancy Pregnancy coincident with heart disease is serious for both mother and child, the maternal mortality is high (3 to 8 per cent), premature birth is frequent. At least 1000 women are said to die annually in the United States from heart disease complicating pregnancy and 90 per cent of the carditis is rheumatic. The maternal mortality in the Toronto General Hospital under such circumstances was 2.3 to 3.4 per cent. Henderson changed the regimen with the result that in a new series of 35 deliveries 46 per cent were spontaneous, 51 per cent were by forceps, 3 per cent only were by cesarean section and sterilization. One patient died from heart failure. Premature birth occurred in seven cases (20 per cent). Once cardiac insufficiency has occurred the maternal mortality is more than doubled, if labor occurs during cardiac failure the mortality is about 50 per cent. Henderson recorded his prenatal regimen, indications for termination of pregnancy and for sterilization, also his management of the various stages of labor.

Recurrences The mechanism underlying relapse is not understood. Poynton and Swift asked: Are they caused by the introduction of fresh infection from some distant focus into susceptible subjects, by some sudden

failure in resistance before the infection is thoroughly destroyed, by some fresh revival of the virulence of the infection which is passing through a phase in its life history? Are they caused by an altered reactivity of tissue so conditioned that slight insults of various types lead to a peculiar mode of response, or by the prolonged residence of some infectious agent in the rheumatic subject, with alternate periods of almost complete immunity and then of diminished resistance?

In 52 per cent of Shapiro's 342 cases of juvenile rheumatism only one attack was experienced, the rest of the patients had recurrences, 54 per cent of them within two years, 17 per cent in the third year, 12 per cent in the fourth year, 3 per cent in the fifth year and 14 per cent thereafter. Until five years have elapsed a patient cannot be too hopeful of escaping a recurrence.

Evidence of Reactivity and Quiescence Ruprecht's criteria of "arrest" included disappearance of subjective signs and symptoms, and normal values for the following: temperature, leukocyte count, Schilling hemogram, nonfilament count and sedimentation rate. Sutton and Dodge gave their criteria for a diagnosis of active carditis.

Bland, Jones and White observed 1000 young patients with rheumatic carditis for 10 years. There was a regression in physical signs in many, a total disappearance of clinical signs of carditis in 83 cases (8.3 per cent).

End Results Twenty-two per cent of Ash's patients with juvenile rheumatism were dead after an average of 7.5 years, and 10 per cent of Shapiro's patients were dead after an average of 6 years of illness. Lesions noted at necropsy were recorded. Banerjee's figures on the mortality of the disease in India agreed with those of Lewis (1933) in England. Relapses occurred in 40 per cent, death occurred within two years in 4 per cent, within 10 years in 24 per cent. Willius' 160 cases, studied until death, included adults, at death 78 per cent had mitral disease, 13 per cent aortic, and 9 per cent both mitral and aortic disease. The first two groups lived an average of 21 years, the third group 16 years after the disease's onset. The disease was rapidly fatal among the Chicago children observed by Gibson and Denenholz, in 40 per cent the first attack of carditis proved fatal. The average age at onset of the disease was 6.3 years, its average duration until death, only 1.4 years. Twenty-seven per cent died within three months of their first rheumatic manifestation.

ETIOLOGY AND PATHOGENESIS OF RHEUMATIC FEVER

Factor of Infection Direct and indirect bacteriologic evidence for the infectious theory were summarized by several (table 1)^{447, 532}

1 *Respiratory Infections* The majority now consider the prodromal respiratory infections to be nonspecific provocatives. Among Shapiro's cases the disease appeared spontaneously in 45 per cent, was preceded by colds in 14 per cent, by a sore throat in 5 per cent, by other factors in 36

TABLE I

Immunologic and Chemical Differences between Rheumatic Fever, Atrophic (Rheumatoid) Arthritis and Hypertrophic (Osteo-) Arthritis *

Test	In normal persons (or other controls)	In rheumatic fever	In atrophic (rheumatoid) arthritis	In hyper- trophic (osteo-) arthritis	Comment significance of test
Skin reactions to nucleoproteins of streptococci	Occasionally + (in 20-40 per cent) Occasionally + (in 20 per cent or less)	Generally + (in 75-80 per cent) Occasionally + (in 20 per cent or less)	Generally + (in 75- 95 per cent) Max- imal reactions com- mon Occasionally + Maximal reactions rare	Generally - Occasionally + Generally -	Significance debatable Positive much more frequently to hemolytic than to green streptococci Not strain specific No definite correlation between skin reactions and agglutination test
	Rarely + Occa- sionally + in non- rheumatic patients	+ in some cases (25 to 50 per cent)	+ in high titer (75- 90 per cent)	Practically al- ways - Rarely +	Significance debatable Reactions are to several, not to one, strain No cor- relation between agglutination tests and the duration, extent, or severity of patient's arthritis Presence of such agglutinins may be attributable to nat- ural rather than to acquired or specific immunity
Agglutinins to <i>Streptococcus</i> <i>viridans</i>	Rarely + (in about 5 per cent)	Rarely + (in 5-10 per cent)	+ in 70 per cent of cases but usually in low titer, occasionally in high titer	Generally - Rarely +	
	Generally none or very few Occa- sionally present in nonrheumatic pa- tients with recent tonsillitis	In about 60 per cent of active cases + In quiescent cases, generally "nega- tive"	+ in 80 per cent of cases (group, not strain, specific)	Rarely + (in 10-20 per cent)	Close approximation, but not an abso- lute agreement, between precipitin and agglutination reactions In rheumatic fever no constant relationship between severity of symptoms and presence of precipitins Precipitin reaction (to hemolytic streptococci) frequently + in various types of arthritis, even gonorrheal
Precipitin reactions to fractions of hemolytic streptococci					

* Figures given are from the recent literature Normal standards in some instances not yet finally established, contradictory results are frequently noted

TABLE I—Continued

Test	In normal persons (or other controls)	In rheumatic fever	In atrophic (rheumatoid) arthritis	In hyper- trophic (osteo-) arthritis	Comment significance of test
Antifibrinolysins (to hemolytic streptococci)	Present in small amounts Present in certain amounts in those without evidence of recent hemolytic streptococcal infections Much increased in erysipelas and other acute hemolytic streptococcal infections	Much increased in 60-70 per cent	Generally not present Occasionally present in cases of early acute arthritis Rarely present in chronic cases		Antifibrinolysins and antistreptolysins are indexes of recent acute hemolytic streptococcal infection Their presence should not be expected in chronic disease
Antistreptohemolysins "antistreptolysins" "antihemolysins" "anhemolysins"	Usually up to 50-100 units Rarely over 150 units Occasionally up to 200-300 units	In about 80-85 per cent of active cases increased markedly (average 500 units) In quiescent cases may not be increased	Only increased (over 150 units) in about 10-20 per cent of cases Later generally not increased	Normal	Significance of antistreptolysins debatable, some say they may be increased in patients with respiratory infections from other than hemolytic streptococci No relation between antistreptolysin titer and agglutination or skin reactions
Streptococcal Complement-fixation test	Sometimes + even in pregnancy and tuberculosiis	In active cases sometimes + In quiescent cases only occasionally +	Usually - according to some, usually + according to others		Significance very debatable Patients may show complement fixation, not only to several strains of streptococci, but also to staphylococci and colon bacilli
Sedimentation rate	Generally below 15 mm (in 1 hour)	Markedly increased May return to normal in cases of congestive heart failure	Almost always increased generally over 30 mm (1 hour)	Rarely over 20 mm (1 hour)	

TABLE I—Continued

Test	In normal persons (or other controls)	In rheumatic fever	In atrophic (rheumatoid) arthritis	In hyper- trophic (osteo-) arthritis	Comment significance of test
Total blood proteins	6-8 gm per 100 c c		Normal	Normal	
Plasma fibrinogen	300-600 mg per 100 c c		Increased	Normal	
Serum globulin	1 2-2 3 gm per 100 c c	Increased	Increased	Normal	Tends to rise in infectious diseases
Serum albumin	4 6-6 7 gm per 100 c c	Decreased	Decreased	Normal, or slightly de- creased	
Albumin-globulin ratio	1 5 1 to 3 1		Frequently below 1 Tends to become nor- mal as patient re- covers	Normal	
Serum calcium	9-11 mg per 100 c c		Normal	Tends to be slightly de- creased	
Plasma cholesterol	160-230 mg per 100 c c		Tends to be decreased	Tends to be in- creased	Tends to fall in infectious diseases, rise in "metabolic diseases"

per cent About 50 per cent of the patients of Gibson and Denenholz noted no prodromal respiratory infections According to Swift, severe pharyngitis or tonsillitis of apparent hemolytic streptococcal origin produces rheumatic relapses in 50 to 60 per cent of previously rheumatic subjects but produces rheumatic symptoms in less than 10 per cent of nonrheumatic subjects The disease has been precipitated by incasles, other exanthems, antismallpox vaccination, injuries, surgical operations, foreign-protein (typhoid) reactions

2 Blood Cultures Blood cultures made by McEwen, Alexander and Bunim on 90 patients with febrile rheumatic polyarthritides were sterile in 83 per cent of cases, positive in 17 per cent, hemolytic streptococci were found in 3 per cent, green-producing streptococci in 13 per cent, indifferent streptococci in 1 per cent Comparing results with those in normal and pathologic controls, they concluded that streptococci cannot be isolated from the blood in rheumatic fever (or in atrophic or other arthritides) more frequently than in miscellaneous diseases Streptococci recovered in rheumatic fever did not differ from those in atrophic arthritis Organisms recovered were probably of no etiologic significance If large quantities of blood and suitable methods are used, streptococci occasionally can be isolated from the blood even of normal persons, but more frequently from those whose resistance is lowered by chronic illness Meyer and Ryan cultured the blood of normal and of rheumatic children, using Kendall's medium, a modification of Clawson's method, and serial transfer technic Insignificant bacteria, mostly diphtheroids, were occasionally obtained from patients and controls All specimens would have been considered sterile by usual methods

Cecil does not believe that the bacteria previously recovered by him were contaminants, too many workers have found them in blood, but their significance is admittedly undetermined Poynton warned that results of cultures of tissues and exudates must be interpreted carefully Unlike suppurative processes that may burst into joints, rheumatic processes do not pour streptococci into fluids As one is not surprised by negative cultures in gonorrheal or tuberculous arthritis, so one should anticipate negative cultures in rheumatic fever

3 Skin Tests Positive skin reactions to hemolytic streptococci were noted by Wasson in 79 per cent of 137 ambulatory rheumatic children, in 29 per cent of nonrheumatic controls There was no relation between the intensity of the skin reaction and the degree of carditis The frequency of positive tests increased with the children's age Retesting showed considerable variability in skin tests on the same patient, due to differences in their general and rheumatic condition

Goldie and Griffiths noted positive skin reactions to hemolytic (but not to green-producing) streptococci three times as often in rheumatic patients as in controls Tests were positive in 77 per cent of 85 cases of rheumatic fever (and in 24 per cent of controls) tested with a concentrated solution of hemolytic streptococci, in 34 per cent of 154 cases (but in no controls)

tested with a less concentrated solution. However, skin tests were generally negative in patients with severely progressive rheumatic fever (as patients with miliary tuberculosis may have negative tuberculin tests). Tests with green-producing streptococci were positive in only 27 per cent of 60 rheumatic patients (and in 24 per cent of controls) with a concentrated solution, and in 3 per cent each of 154 rheumatic cases and 30 controls with a less concentrated solution.

4 *Streptococcal Agglutinins* Positive agglutination tests with hemolytic streptococci (titer 1 to 20 or over) were found by McEwen, Alexander and Bunim in none of 35 normal controls, in only 5 of 71 patients with rheumatic fever (titer 1 to 20 in one, 1 to 40 in two, 1 to 80 in three). Thus these workers did not confirm Coburn and Pauli's observation (1932) that serum of most patients with acute rheumatic fever agglutinated hemolytic streptococci to a titer of 1:10 to 1:40. Goldie and Griffith found agglutinins to hemolytic streptococci in a titer of 1:100 in 80 per cent of rheumatic fever patients, in 10 per cent of controls, agglutinins to green-producing streptococci in a titer of 1:100 in only 6 per cent of rheumatic cases, in 5 per cent of controls.

5 *Antifibrinolysins* Patients convalescing from diseases due to hemolytic streptococci generally possess antifibrinolysins, that is, the fibrin in their sera is markedly or completely resistant to fibrinolysis, or liquefaction of blood clot, by cultures of hemolytic streptococci. Confirming the work of others^{245, 246, 247} Stuart-Harris noted antifibrinolysins in the blood of patients with rheumatic fever (but not with atrophic arthritis) particularly during the acute stage or after intercurrent streptococcal infection during convalescence from activity. Thus he considered rheumatic fever (but not atrophic arthritis) related to hemolytic streptococcal infection. The findings of McEwen, Alexander and Bunim were similar, complete resistance to dissolution being noted in 59 per cent, marked resistance in 14 per cent, of 29 patients with rheumatic fever.

6 *Hemolytic Streptococcal Precipitation Tests* Antigenically hemolytic streptococci are complex mosaics containing, among other fractions, a "nucleoprotein" (P fraction) which is not specific as it gives cross precipitation with other gram-positive cocci, a group-specific carbohydrate (C fraction), and type-specific protein and carbohydrate fractions (M and S fractions). Hemolytic streptococci are known to induce the formation, not only of antistreptolysins and antifibrinolysins, but also of two other antibodies, anti-C precipitins and anti-P precipitins. These four antibodies have been demonstrated in the serum of patients with various streptococcal infections. Because they have also been found by some workers in a high proportion of patients with rheumatic fever it has been suggested that there is a close connection between streptococcal infection and this disease. McEwen, Alexander and Bunim, and Chasis and McEwen noted precipitin reactions to crude "C" extracts (fractions) in 56 per cent of 39 patients with rheumatic fever but also in a fairly high percentage of patients with

other articular diseases and in 24 per cent of normal controls. Highly positive reactions were noted equally in those with rheumatic fever or with atrophic arthritis, less frequently in controls. The test therefore was of no differentiating value, an opinion concurred in by Race.

Swift and Hodge studied the development of type-specific anti-M precipitins in two groups of patients suffering with hemolytic streptococcal infections. Most of the patients in group I, none of whom developed rheumatic fever, showed relatively strong type-specific reactions in their serum within four to five weeks. Those in group II all developed rheumatic fever, some had similar strong antibodies early, but most rheumatic patients from whom hemolytic streptococci were cultured in significant numbers from various foci, did not show strong anti-M precipitins until distinctly later than the nonrheumatic group. Swift has repeatedly been unable to show a constant relationship between the severity of symptoms of patients with rheumatic fever and the presence of precipitins against either the "C" (carbohydrate) or the "P" (nucleoprotein) fractions of group A hemolytic streptococci.

7 *Antistreptolysins* ("Antihemolysins" "Anhemolysins") The upper limit of normal was regarded by earlier workers to be 50 units of anti-streptolysin, by later workers to be 150 units^{245, 246, 247}. The establishment of the new level made the test more specific but at the cost of reporting "normal values" in 24 to 30 per cent of cases of rheumatic fever, with titers between 50 and 150. Race believes the upper normal level should be re-established at 50 units. Eighty per cent of 51 rheumatic fever patients (but only 3 per cent of 37 normal controls and 12 per cent of patients with atrophic arthritis) showed 150 or more units of antistreptolysin, according to McEwen and colleagues. However, the titer did not rise above 25 units in one unquestionable case studied over two months. Goldie and Griffiths noted "abnormal values" (over 50 units) in 100 per cent of 40 cases of "rheumatic fever with chorea," in 88 per cent of 154 cases of subacute rheumatism, in 20 to 27 per cent of two sets of controls. Values of 100 + units were found in 92 per cent, 58 per cent and 3 to 8 per cent respectively, 200 + units in 80 per cent, 35 per cent and 0 to 2 per cent respectively. Longcope regarded 100 units as the limit of normality. The antistreptolysin titer was above 100 units in 85 per cent of his cases of acute rheumatic fever, in 86 per cent of cases of chorea, in 80 per cent of cases of erythema multiforme and nodosum, in 28 per cent of cases of "chronic inactive rheumatic heart disease," in 46 per cent of cases of atrophic arthritis. It was over 200 units in 51 per cent, 50 per cent, 60 per cent, 0 per cent and 18 per cent of these same groups respectively. Contrary to the experience of Coburn and Pauli (1935), in Longcope's series the height of the titers did not parallel the severity or duration of acute attacks of rheumatic fever. High titers in this disease should be regarded as the result of a recent hemolytic streptococcal infection but "cannot be used as evidence that [rheumatic fever] is caused by hemolytic streptococci."

Correlation and Interpretation of Immunologic Data The significance

of these data is incompletely understood (table 1) Little has occurred to change the interpretation of the main features as given in the third review Space does not permit the inclusion of reported explanations of the conflicting data and reference must be made to the reports cited Coburn's correlation still seems the clearest, whether correct or not it is the most positively stated It seems to do much to explain the basis for the conflicting opinions (for example, that of Coburn and Wilson) reported in previous reviews It attempts to show why some pharyngeal infections never produce initial or subsequent rheumatic attacks, why some hemolytic streptococcal infections sometimes do and sometimes do not (even in rheumatic subjects) produce attacks, and why rheumatic attacks are generally but not always precipitated in susceptible individuals with the production of antistreptolysins

To clarify the mechanism of its production one must divide the rheumatic process into its three clinical phases which, although symptomatically distinct, are interdependent stages of a specific set of immunologic reactions Each phase must be considered separately, yet sequentially The first phase, that of acute upper respiratory tract infection, lasts only a few days But in this phase are set in motion factors which may or may not eventuate in the rheumatic explosion The second phase follows immediately after the respiratory infection, is characterized by a complete absence of clinical symptoms and signs, and lasts from a few days to about six weeks, generally one to two weeks Although this phase is symptomless it is crucial, for during it, processes initiated in the first phase come to maturity, if they mature in one way, normally as they usually do, a rheumatic attack does not materialize, but if they mature in another way, abnormally, a rheumatic attack of variable severity results The third phase begins with the onset of rheumatic manifestations and varies widely in the duration and intensity of its symptoms

The hemolytic streptococcal infection (pharyngitis) of phase one is nonspecific in at least certain ways, the rheumatic patient is no more or less susceptible to it than the nonrheumatic patient The clinical characteristics of the pharyngitis are the same in the rheumatic and the nonrheumatic, the upper respiratory tract of the rheumatic patient may be infected with the same strains of hemolytic streptococci as that of the nonrheumatic, and the pharyngeal infection has the same variable persistency in the nonrheumatic as in the rheumatic patient Why then does one patient get acute rheumatism and the other not? A crucial difference lies in the type of immune response which the infection generates, furthermore, the chief difference in type is not just a difference in the content of the immune response but in the speed of its development If an immune reaction to the phase-one infection fails to develop (as it may in either the rheumatic or nonrheumatic patient) or if it develops in the second or silent phase, with normal promptness, no rheumatism results in the normal person or even in one previously rheumatic, and the third phase never materializes But if an immune reaction, engendered by phase one, develops tardily in phase two, with abnormal slowness, then rheumatic fever results The basis of this concept follows

The potent types of pharyngitis (as far as the production of rheumatic fever is concerned) are commonly due to hemolytic streptococci, Lancefield group A As they pertain to rheumatic fever they are group but not strain specific These hemolytic streptococci produce two or more soluble antigens (soluble bacterial derivatives or exotoxins) and at least three other antigens (intracellular bacterial derivatives or endotoxins) The two well-recognized soluble antigens are (1) an erythrogenic toxin, probably capable of damaging vascular endothelium and against which the

body generally forms neutralizing antibodies which cause the patient to be "Dick-negative," and (2) streptolysin which the body attacks by the production of anti-streptolysins—antibodies which are specific for hemolytic streptococci, probably group specific, which are quantitatively measurable by titration and which are recognized as bona fide evidences of recent hemolytic streptococcal infection

The three other recognized antigens (intracellular bacterial derivatives) produced by hemolytic streptococci are (1) a type-specific protein, called M-substance or M-extract, against which the body during a rheumatic attack forms "precipitins to M-substance" which can be detected qualitatively in serum, (2) a nucleoprotein called P-substance, against which the patient's body frequently develops "precipitins to P-substance," the presence of which is demonstrated by positive skin reactions to hemolytic streptococcal nucleoprotein, and (3) a group-specific carbohydrate or C-substance, precipitins to which the patient's body develops and delivers to serum

Still another protective substance found in the blood of patients with rheumatic fever or with definite hemolytic streptococcal infections is antifibrinolysin

The relative importance of these antigenic substances and what pathologic reactions they induce or could induce in the body were they not neutralized by antibodies has not been fully determined. It appears, as one might expect, that erythrogenic toxin and streptolysin are released at the onset of infection whereas the M-substance and nucleoprotein P-substance are liberated after the disintegration of bacterial cells. According to Coburn the antistreptolysin curve (its quantity and speed of development) shows the patient's response to infection. He feels that an understanding of the abnormal response may help to elucidate the mechanism of an attack

The silent phase two varies considerably in length but its duration appears to coincide with the time required for the appearance of the antistreptolysin response in rheumatic patients. Coburn noted previously that in a group of rheumatic subjects infected with a single strain of hemolytic streptococcus those that developed acute rheumatism developed an antistreptolysin response, while those who failed to make this response escaped an attack. He noted that a rheumatic patient who contracts a series of hemolytic streptococcal infections develops acute rheumatism only when the infection is followed by a rise in antistreptolysin titer. In the absence of an antistreptolysin response there was no rheumatic attack. He then studied the comparative alterations in the erythrocyte sedimentation rate and the antistreptolysin titer in 100 patients with rheumatic carditis in relation to different stages of phase three

At the onset of symptoms the sedimentation rate and antistreptolysin titer both rise, at the height of the attack the rate is at its maximum but the titers still rise. When symptoms begin to subside the rate is still at its maximum, the titer is either at its maximum or still continues to rise. As symptoms continue to subside the rate falls but there is a lag in the fall of the titer, the titer may stay at its maximum

the initial symptoms appeared with the appearance of the antibody but the curve of subsequent symptoms did not parallel the antibody titer

After different hemolytic streptococcal infections the time when the maximum concentration of antistreptolysins occurs varies widely. In acute rheumatism maximum titers rarely occur within five weeks, in protracted cases they are not usually reached until several months after the hemolytic streptococcal pharyngitis. This is in sharp contrast to what obtains in erysipelas, for example, where the peak-titer is reached within 20 days after the onset of infection. Coburn found that the clinical character of the rheumatic attack varied with the shape of the antistreptolysin curve. The sooner a patient developed a maximal titer, the sooner he recovered. In other words those curves which approached normal responses (an early rise and fall) were

associated with short or mild attacks. In contrast, those characterized by an abnormally slow rise were associated with a prolonged severe carditis. Apparently then the crucial characteristic of the rheumatic candidate may be a delay in his immune response to hemolytic streptococci. As stated, following a hemolytic streptococcal infection a nonrheumatic person either (rarely) develops no rise in antistreptolysins or generally develops a prompt response with a maximal antistreptolysin titer within 20 days. If the rheumatic subject makes either of these two responses he escapes an attack. That is, if there is no antistreptolysin response there is no attack, or if the increased antistreptolysins appear promptly and reach their maximum early and normally (within 20 days) there is no attack. But if, as frequently happens, the rheumatic patient develops an intense delayed antistreptolysin response a week or more after the normal response should have occurred, acute rheumatism develops.

In conclusion, Coburn stated that until now there has been no evidence whether the antistreptolysin curves seen in rheumatic fever were normal responses to hemolytic streptococcus infection or not. His data would indicate that the immune responses of the rheumatic patient differ from the normal chiefly in that they are delayed. This being so it may be assumed that the rheumatic subject who develops an attack handles the products of hemolytic streptococci peculiarly, involving a delay in the final elimination of hemolytic streptococcal products from the body. Why such a delay occurs or how it is associated with the development of the disease is undetermined.

Factor of Bacterial Allergy Poynton's simple interpretation of what is presumably meant by bacterial allergy seems worthy of inclusion.

Assume that an infected focus is a streptococcal depot more or less constantly pouring into the circulation the body-protein of streptococci, which acts as a foreign body circulating in the human system. Such foreign substances stimulate the production of specific antibodies, hence are called "antigens." Antigens arising in a focus of infection and circulating in the body will stimulate certain tissue cells to produce antibody and in doing so this will sensitize these cells. If the response to antibody is prompt and abundant a surplus of this antibody will appear in the circulation and from now on antigen escaping from the focus of infection will meet this surplus antibody in the blood stream and be neutralized there, consequently will not reach the tissue cells. But should the production of antibody be deficient and there be no surplus in the blood stream, but the whole amount be kept back in the producing cells, a different situation arises. The continuous supply of antigen from the focus of infection has then no antibody meeting it in the blood stream, and hence will not be neutralized there but will once more reach the cells which, however, now contain a store of antibody. The antigen then combines with the antibody in the cells and this clash of antigen and antibody will irritate those cells. Thus this antigen, which was formerly innocuous to the cells when they contained no antibody, now acts as a cellular poison to them because they contain antibody. Such reactions are called hypersensitiveness or allergy. Under the theory of bacteremia or bacterial toxemia as the cause of rheumatism (which Poynton espouses) it is supposed that streptococci by their presence or by their toxins produce the local articular (and other) lesions by local infections, but the theory of bacterial allergy assumes that the antigens (streptococcal products) are not toxic per se unless or until they clash with antibody in the tissue cells.

Swift's concept of rheumatic fever as a manifestation of bacterial allergy

is well known, has been discussed herein before^{240, 246, 247} and needs no detailed repetition. He considered it obvious that rheumatic fever patients are unusually hypersensitive to many different injurious agents, but mostly to streptococci. Although all the possible relationships between hyperergy and rheumatism have not been explored the concept clarifies much that seems inexplicable otherwise. However, Schlesinger found it difficult to explain valvular vegetations and pericardial "bread and butter" exudate purely on an allergic basis. He regarded those who believe allergy to be the fundamental cause of rheumatism "still somewhat hazy in their reasoning." "A much stronger case will have to be made out for allergy before such striking, marked changes are regarded as anything but the inflammatory result of an infective agent at the site."

Virus Theory The isolation of "virus bodies" from exudates of rheumatic patients was recently reported but the disease had not been experimentally reproduced²⁴⁷. Swift raised two objections to the theory. 1 Filtrable viruses apparently do not produce fibrinoid degeneration, a basic pathologic feature of the disease. 2 No virus for rheumatic fever has been definitely discovered. The results of Swift's 15 years' search for such a virus were essentially negative, methods by which he sought them were briefly summarized. Either virus was not present in material used or the various animal species tested were not susceptible. Nevertheless a possible symbiotic relationship between virus and bacteria must be borne in mind. Possibly an allergic state makes the tissues susceptible to a hypothetical specific virus, or vice versa, possibly such a virus may cause an allergic state so that bacterial infection or other traumatic insult sets off an acute attack.

Synergism of Infection and Vitamin C Deficiency Rinehart restated his concept that the disease may be due to the combined influence of vitamin C deficiency and infection (as discussed previously in Reviews 2 and 3). It is based on the experimental production of subcutaneous nodules, cardiac and articular lesions, "comparable to those of rheumatic fever" (and to a certain extent of atrophic arthritis), in guinea-pigs subjected to the influence of both infection and vitamin deficiency, but not in those subjected to either factor alone. He further noted a borderline or frank vitamin C deficiency in the diets of most rheumatic children. Plasma ascorbic acid levels usually parallel the vitamin C intake²¹⁸. Rinehart, Greenberg and Christie noted a lowering of plasma ascorbic acid in almost all of 21 patients with acute rheumatic fever, in many with the disease quiescent. It has not been determined whether the reduction was due to inadequate intake, or to the anorexia, digestive disorders or depletion by the disease itself.

Various cardiac and articular lesions were produced by Schultz in guinea-pigs subjected to infection and experimental scurvy, alone and in combination. Infected scorbutic animals developed focal interstitial valvulitis, fibrinoid degeneration, occasionally focal, nonpurulent myocarditis. Non-infected scorbutic animals developed lesions similar but of less extent. In

either case Schultz regarded them as only slightly resembling those of rheumatic fever. No verrucous endocarditis was seen and the myocardial lesions were few and did not closely resemble Aschoff bodies. Scorbutic changes were noted in and around joints but were not enhanced in the infected animals. In 8 of 13 patients with rheumatic fever, some degree of ascorbic acid deficiency was noted by Sendroy and Schultz. It was ascribed to poor diets in two instances, to vomiting or incomplete absorption in six cases. They concluded that ascorbic acid deficiency is not specific for rheumatic fever, is probably incidental in this disease, and did not seem to be a predisposing factor.

Conclusions on Etiology Although interested in the conjecture that the disease represents a symbiosis between virus and streptococci, Schlesinger did not regard any current theory with satisfaction. The so-called specific streptococci of Poynton and Paine, Birkhaug and Small do not produce lesions characteristic of the human disease and are found in the throats of nonrheumatic persons. Hemolytic streptococci are not present in the throats of normal persons, but some patients severely infected therewith do not get rheumatic fever and the disease is obviously not precipitated by a specific strain. Reviewing his own work and that which has followed it, Poynton concluded that the cause of the disease is a diplostreptococcus of a special type (which on various media appears as a streptococcus, or even a staphylococcus), a constitution of a special type, a focus of infection, an invasion of the system by streptococci and the formation of foci of a peculiar type within the body in "the connective tissue skeleton" and the development of poisons injuring the "noble tissues," heart, brain and so forth. "The future must decide whether [streptococci] are gangsters, or the accessories of gangsters, or just the watching crowd always in the way and never doing anything themselves, a rôle not peculiar to streptococci."

TREATMENT OF RHEUMATIC FEVER

Treatment remains essentially as before. Its general principles were reviewed by many^{527, 532}

Bed Rest This should be continued after all symptoms have disappeared, for at least two weeks in those without evidence of carditis, for months (6 or more), not weeks, in those who develop carditis^{461, 577}. It should be continued until the patient has gone six to eight weeks with no signs or symptoms of disease and with a normal sleeping pulse rate (well below 90 per minute)²². Adequate rest involves the use of appropriate sedatives.

Salicylates Salicylates are still considered "extremely useful"^{22, 461}. Some believe they shorten the disease and minimize danger to the heart³⁵³. Others believe they do not affect the proliferative reactions, for which drugs are of little value. But the action of salicylates on the exudative features of the disease is almost specific and diagnostic, affecting other types of fever

or effusion in no comparable manner¹³⁸ One must not conclude that the disease is necessarily inactive when fever is controlled by salicylates, Poynton disapproved "desperate efforts" to lower temperatures thereby Some used large,³⁵³ others used smaller doses⁵⁶ Kaisei concluded that acetylsalicylic acid, combined with magnesium oxide, was superior to salicylates alone in controlling joint pains and chorea and, in preventing recurrences, but not in relieving carditis

Other Drugs Poynton preferred tolysin to salicylates Pyramidon was used by some,⁵⁶ avoided by others for fear of granulocytopenia⁷ Some considered digitalis valuable in congestive failure, useless in controlling tachycardia²² Although it occasionally slows the pulse and improves circulation its results are disappointing unless fibrillation is present¹³⁸

Removal of Tonsils and Other Foci Kaiser summarized the effect of tonsillectomy on 48,000 rheumatic children Tonsillectomized children are less likely to develop subsequent rheumatic fever and carditis, but as likely to develop muscular rheumatism and chorea as those who retain their tonsils However, the incidence of recurrent attacks of rheumatic fever is not influenced by tonsillectomy done either before or after an initial attack Tonsillectomy does influence end-results of the disease The mortality was nearly twice as high among children in possession of their tonsils at the initial attack as among those tonsillectomized before their initial attack "Tonsillectomy is justified in practically every rheumatic child until other factors that influence this disease are better understood"

When performed, tonsillectomy should be done after the acute phase of the disease,⁴⁵⁵ and only when there is evidence of diseased tonsils¹³⁸ Even then it should be considered a major operation with preoperative and postoperative bed rest^{353, 521} The danger of exacerbations after tonsillectomy can be "greatly lessened" by the daily administration of acetylsalicylic acid for one month after tonsillectomy⁷ Wallace and Smith found no evidence that the very early removal of tonsils of children (before the age of five years) protected them against rheumatic fever

Vaccines The use of streptococcal vaccines was "unsound," according to some,⁷ useless according to others Stroud gave vaccine intravenously to children for three years those vaccinated did no better than the unvaccinated

Serum Hoping that the blood of patients recovered from rheumatic fever might contain enough antibodies to help those with active disease, Archer treated four patients intrathecally with small doses of convalescents' serum Results were "suggestive enough" to warrant further clinical trial

Transfusions Weiss noted "satisfactory results" from the use of multiple small (150 to 250 c c) citrate transfusions Results in one case were reported, others were to be reported later

Vitamin C Many of the rheumatic children studied by Rinehart were on a diet low or frankly deficient in vitamin C Preliminary results from

diets rich in vitamin C were "encouraging" Many patients gained weight, a number suffered respiratory infections without rheumatic exacerbations However, the oral administration by Schultz of 100 mg of ascorbic acid (redoxon) daily for several months to 28 rheumatic patients did not lower the incidence of subsequent rheumatic activity as compared to a control group treated by lactose Another group of 17 patients with active rheumatic fever were given 250 mg of ascorbic acid daily by mouth or intravenously for from one to five (average 2.5) months, some were also given 200 c c orange juice daily The disease was not affected thereby Wright also was unable to affect the course of the disease by giving cevitic acid (ascorbic acid, crystalline vitamin C) in doses as large as 1000 to 2000 mg intravenously daily Rhinehart does not believe that lack of response to vitamin C therapy necessarily disproves the etiologic importance of vitamin C deficiency, the latter may be only one factor in preparing the soil for infection But Wright believed that the disease, if related to a deficiency, should be ameliorated to some degree by such large doses

Fever Therapy The chorea of 16 children with active carditis was being treated with foreign-protein fever by Sutton and Dodge Nine of the children lost signs of activity during the course of treatment, in the rest the carditis was clinically inactive within seven to ten days thereafter Subsequently, seven patients with subacute carditis without chorea were treated with artificial fever (two to five hours, at 105° to 106° F for one or two sessions), soon thereafter signs of active carditis disappeared or notably diminished Further investigation seemed warranted

Additional Therapy for the Heart Severe angina pectoris may occur in young people with rheumatic carditis Attacks may appear at night, recumbency seems to precipitate them Good results (better than in arteriosclerotic angina) were obtained by Bland and White in four such cases by paravertebral injections of procaine and 95 per cent alcohol, blocking sympathetic rami of the first four dorsal roots Left-sided injections were usually effective, bilateral injections were occasionally made

Institutional Care, Climate Active subclinical carditis may long persist, sometimes even with a normal sedimentation rate (Sutton) Therefore prolonged observation and care are required before and after patients are returned to their homes, to activity and to school life Rheumatologists and cardiologists are heartily approving convalescent and rest homes, sanatoria for the prolonged supervision of convalescence, and schools for "cardiac cripples" as an important intermediary between hospital care and an active routine which, begun too early, may provoke exacerbations^{439, 455, 465} By such "rheumatism schemes" as that in Cardiff⁴⁹³ or that of the London County Council cooperating with voluntary hospitals and rest homes, much has been done to "commute the sentence of death" from rheumatic fever The established institutions and "cardiac schools," however, cannot deal with more than a fraction of the cases, and it is impossible to send most patients for a prolonged stay in the tropics^{133, 332}

Prophylaxis The multiplication of convalescent homes, special clinics, and rheumatism supervisory centers may prevent more deaths, but not the disease McSweeney called it "philanthropy not prophylaxis" Current methods for prophylaxis are inadequate as the incidence of the disease shows There is therefore great need for the institution of an active, sustained crusade against the disease, following general principles similar to those so successfully employed against tuberculosis This involves better personal and social hygiene, more effective child welfare schemes and school medical service under which physicians and nurses exercise closer supervision over children's health Rheumatic fever should be a notifiable disease, notification would permit subsequent sociologic and epidemiologic studies of the greatest importance (Ritchie)

SYDENHAM'S CHOREA

Chorea accompanied rheumatic fever in 5 to 34 per cent of recent cases, it was an initial symptom in many (21 to 28 per cent) ^{11, 85, 197, 572} It was rare in India ⁸⁰ Statistics indicated that chorea per se is a mild manifestation of rheumatism but may be associated with severe, even fatal, carditis ^{11, 197}

Most writers agreed that chorea is most commonly caused by rheumatic fever but can be precipitated by other factors fright, chilling, emotional shock, fatigue Smith and Markey stressed the emotional factor, Guttmann noted its incidence with psychoses Poynton regarded rheumatism the main, fright a rare, cause, fewer London children had chorea the year of the terrifying war-bombings than the following year

In acute chorea Payne and Schlesinger noted either no rise of the sedimentation rate (in 44 per cent of cases) or only a slight transient rise (in 56 per cent) It was no index of choreic severity or of impending carditis Indeed rates were often very low Struthers and Bacal noted normal sedimentation rates and Schilling counts

Treatment Large doses of phenobarbital controlled a case of severe chorea of 4 5 months' duration in a child, aged 11, seen by Litchfield, Gillman, Harris and Cohen During four weeks' treatment the dose was gradually raised from 1 5 to 22 grains daily without toxicity Smith considered nirvanol therapy drastic, sometimes dangerous because of its effect on bone marrow

Several reports testified to the superiority of fever therapy over other methods Of 50 patients treated by Weisman and Leslie with fever reactions from typhoid vaccine 46 became symptom free, two improved, two did not, only five patients had recurrences within three years Treatments were given daily for seven to eight days, omitted two to four days, then continued as necessary Generally eight or nine fever reactions (to 104° or 105°, occasionally 106° or 107° F) were given, the greater the fever, the better the results Those with active carditis seemed to do as well if not

better than others. Results of similar treatments were excellent in six, poor in two, of eight cases seen by Litchfield and his colleagues. Fever reactions to 104° or 105° F were induced daily for 7 to 12 days.

The results of Sutton and Dodge were even more striking. Among 150 patients treated by orthodox methods the average duration of chorea after therapy was begun was 43 (10 to 180) days. Of 150 patients treated with triple typhoid vaccine symptoms averaged only 9 (2 to 47) days after treatment. Vaccine injections were given daily, with an occasional rest day, until chorea stopped. The number of injections averaged five in mild cases, six in moderate cases, nine in severe cases (maximum 18). Because typhoid vaccine fever reactions are not as controllable as artificial fever, 16 other patients were treated with the latter (radiant energy). Results from only one or two artificial fever sessions were as good as those from several vaccine-fevers. Subacute carditis was not a contraindication, indeed it seemed to be relieved.

Excellent results from artificial fever were noted by others. All of 13 patients treated by Barnacle, Ewalt and Ebaugh were "cured." No recurrences were noted within one year. Six cases of "most severe" chorea of two weeks to 10 months' duration were slowly but completely stopped by similar treatments given by Metz. Symptoms disappeared within two to four weeks. Neymann, Blatt and Osborne also noted excellent results from fever (electro-magnetic induction) in 25 cases, nine very severe, six moderate, ten mild. From two to ten (áv four) treatments were given, two per week. Recurrences occurred in 12 per cent. Complications were a heat convulsion in one case, transient albuminuria and hematuria in one case.

CHRONIC ARTHRITIS

General Remarks on the Relationships and Distinctions between the Two Great Types. Those who espouse the "unitarian idea" consider atrophic and hypertrophic arthritis varieties of one disease, differences being due chiefly to the factor of age, physiologic rather than calendar. To them atrophic arthritis represents the reaction of physiologically young tissues against an insult, hypertrophic arthritis is the reaction of physiologically aging tissues against the same insult. Others, more equivocal, believe the two great types are very closely related etiologically, but are probably different diseases. Some believe that both types of chronic arthritis are often the result of similar factors.^{279, 380} Most rheumatologists, however, stress the distinctions between the two types and consider them totally unrelated diseases, "sharing little but a common battleground."^{165, 223, 388} Citing the manifold constitutional, clinical, cytologic, chemical, immunologic, pathologic, roentgenographic and prognostic differences between them they would conclude with Boots: "There would now seem to be no further excuse to look upon these cases as examples of a single disease." The frequency of patients with mixed (clinical, not just radiologic) types, who demonstrate

both atrophic and hypertrophic arthritis in different or even in the same joint, does not confuse those who realize that every young or middle-aged patient with atrophic arthritis will, if he lives long enough, develop hypertrophic arthritis, since the latter is a histologic (although not necessarily a symptom-producing) inevitability to all persons over 50 or 60 years of age. Then too, patients over 50 years of age with hypertrophic arthritis are not immune to atrophic arthritis which even the elderly may develop independently of their coincidental hypertrophic arthritis.

Clinical and Pathologic Distinctions The familiar clinical and pathologic distinctions between atrophic and hypertrophic arthritis were again reviewed ^{48, 194, 195, 200, 300}

Cytologic, Chemical and Immunologic Differences These were again summarized ^{83, 130, 243} (table 1)

Roentgenographic Differentiation According to S. G. Scott clinical diagnoses of the chronic arthritides can be made with considerable accuracy from roentgenograms alone, particularly of hands. Others^{4, 172, 177, 504, 535} regard roentgenographic differences as highly suggestive but not pathognomonic. They believe that a final clinical diagnosis cannot be based on roentgenograms alone, features of the latter must be correlated with clinical and biochemical findings. Although osteophytes are much commoner in hypertrophic arthritis, they are frequently seen in late atrophic arthritis, especially in weight bearing joints, or they may occur in almost any infectious type of suppurative or nonsuppurative arthritis. A radiologist, noting these osteophytes and having no knowledge of the clinical features, will often classify such a case as hypertrophic arthritis (a diagnosis correct in the radiologic sense but incorrect in a clinical sense) ¹⁷⁷

The comparative radiology of the two great types was noted by several ^{5, 172, 504, 535}. Taylor and his colleagues noted the following: marked systemic decalcification in 95 per cent of cases of atrophic, but only mild decalcification consistent with age in 75 per cent of cases of hypertrophic arthritis, also local decalcification in 13 per cent and 6 per cent, respectively, bone production (lippling and osteophytes) in 77 per cent and 100 per cent, "atrophic bone destruction" (punched-out areas) in 85 per cent and 9 per cent, "active bone destruction" in 11 per cent and 0 per cent, cartilage destruction (narrowing of joint space) in 95 per cent and 59 per cent, fusiform enlargement of soft tissue in 88 per cent and 9 per cent. Ankylosis occurred in 26 per cent of the atrophic, in only 6 per cent of the hypertrophic cases, in the latter only in the spine. Although individual features were shared by both types of arthritis, each possessed a basic pattern or grouping of features which makes roentgenograms very helpful in differentiation. The two types are radiographically distinct, even when they coexist in the same joint.

An appraisal of the diagnostic worth of the finer radiologic differences was made by Spackman who studied 1000 cases of chronic arthritis in patients aged 9 to 76 years: 474 with atrophic, 526 with hypertrophic arthritis.

Asymptomatic cases of the latter were not included. Changes in atrophic arthritis were as follows: in the early stage there were rarefaction of the trabeculated ends of bones, preservation of the zone of provisional calcification but irregularities therein, homogeneous haziness at joint space, at first widening, later narrowing of joint space. The earliest recognizable change was roughening or slight irregularity of the zone of provisional calcification, very minute projections of new bone into cartilage and small irregular areas of decreased density especially in the proximal border of the zone. In intermediate and late stages there was progressive ground glass atrophy, soft tissue swelling, disappearance of the line of provisional calcification and bony ankylosis of the joint. Changes in hypertrophic arthritis were as follows: in the early stage there were small, marginal osteophytes, narrowing of joint space, change in alignment of bones, thickening of the provisional zone of calcification, irregularity of the bony articulating surfaces, broadening of the circumference and secondary atrophy of the honey-comb type, in the intermediate and late stages, spur formation, Heberden's nodes, eburnation of bone, displacement and subluxation, punched-out areas, gross deformity and advanced secondary atrophy.

Morrison and Kuhns studied 55 cases of atrophic, 11 of hypertrophic and 7 of "mixed arthritis" to note the changes in serial roentgenograms taken from four to ten years or more apart. The changes varied greatly in different patients and in the same patient at different ages, and at different stages of the disease. The changes in atrophic and hypertrophic arthritis were not pathognomonic, and differed from those in the more acute and specific arthritides chiefly in the slow rate at which the former progressed. Marked changes were compatible with good function. Even though the radiologic changes were increasing, good functional recovery was possible. Changes in roentgenograms usually progressed long after the disease was clinically quiescent. Improvement in the roentgenologic picture was rarely seen, recalcification of bone and moderate repair were observed in the roentgenograms of only two patients. On a radiologic basis, Scott subdivided atrophic arthritis into "rheumatoid arthritis" and "infective arthritis," general decalcification being the keynote of rheumatoid arthritis, loss of cartilage with early bone sclerosis at the affected joints being the feature of infective arthritis. Others^{4, 535} found no radiologic basis for such a subdivision of atrophic (rheumatoid) arthritis. Aldred-Brown and Stevens did notice two "varieties," some with dominant local changes, others with dominant systemic bone changes. But they often occurred together and there was no evidence that the one type was associated with infection, the other, not.

Constitutional Differences, Anthropometric, Psychologic. Some affirm, others deny that atrophic arthritis occurs chiefly in the asthenic, and osteoarthritis in the pyknic, type. Anthropometric studies by Kovacs, Hartung and Hanscom on 50 patients with atrophic and 50 with hypertrophic arthritis revealed marked differences in constitutional morphology. Those with at-

rophic arthritis had a tendency to increased longitudinal measurements, longer and thinner necks, slender but not necessarily tall build, with weights normal or subnormal. Those with hypertrophic arthritis had a tendency to obesity, increased horizontal measurements, short thick necks, massive silhouettes.

(These 100 patients were all females, it would be interesting for the same investigators to make identical studies on males—Ed.)

Psychologic differences between patients with atrophic arthritis and those with hypertrophic arthritis were noted by Ellman and Mitchell, but not by Kovacs, Hartung and Hanscom.

ATROPHIC ARTHRITIS

Incidence Factors influencing the incidence of this disease are similar to those which influence rheumatic fever. Atrophic arthritis rarely appears among native whites or Indians in the Arizona desert.²⁶⁹ Winter produces its harmful effects by cold and damp, not by cold alone.⁶⁹ The patient's resistance is lowered by overheated houses and excess clothing, by the greater incidence of colds and tonsillitis which may provoke the disease and by a lack of adequate exercise and sweating. The peak incidence in the cases of Dawson and Tyson was between February and April. The disease is rare in children, only 10 of 800 patients seen by Dawson and Tyson were under 12 years of age. Among Pemberton's 300 patients of all ages 3 per cent were children. To Irons the influence of heredity seemed obvious; the disease often appeared in grandmother, mother and daughter. In Dawson and Tyson's series the familial incidence was 15 per cent.

Symptoms and Course Some English writers spoke of two varieties: 1 "Primary rheumatoid arthritis" or "rheumatoid arthritis" is of insidious afebrile onset and is accompanied by no marked inflammation and no obvious or related foci. 2 "Secondary rheumatoid arthritis," "chronic infective arthritis," or "focal arthritis" usually is of acute or subacute febrile onset and is accompanied by considerable inflammation and obvious foci to which it is supposedly secondary and after removal of which notable improvement is expected. Because the basis for complete separation of these two varieties is not clear, the American Rheumatism Association has not recognized such a subdivision of atrophic (rheumatoid) arthritis.

Complications Cardiovascular disease occurs only with the expected frequency in patients with atrophic (but with increased frequency in those with hypertrophic) arthritis, according to Monroe and Walcott. In 142 patients with atrophic arthritis cardiac enlargement occurred in 6 per cent, hypertension in 10 per cent, arteriosclerosis in 11 per cent, varicose veins in 5 per cent. Cardiovascular decompensation was rare, angina pectoris did not occur in this series.

Rheumatic iridocyclitis occurs not infrequently in children with chronic

polyarthritis, it often has a chronic course, causing ribbon-like keratitis Holm reported a case in a 15 year old gull with Still's disease (adenopathy but no enlargement of liver or spleen) The probable rheumatic nature of primary juvenile iridocyclitis should be kept in mind In such cases the iridocyclitis may come before, with, or after the arthritis

Atrophic Arthritis and Splenomegaly, Still's Disease, "Felty's Syndrome" The association of arthritis with splenomegaly, sometimes with adenopathy, hepatomegaly, anemia and leukopenia or leukocytosis was described by Chauffard and Ramond (1896), Still (1897) Herringham (1909) and others, more recently by Felty (1924) The third review contained comments on the relationship between these syndromes, particularly on whether Felty's syndrome was different from or identical with Still's disease Williams reported a case of Felty's syndrome with necropsy findings, he considered it not identical with Still's disease, but a blood dyscrasia in which there is an arrest in the maturation of polymorphonuclear leukocytes Singer and Levy, who also reported two cases with necropsy findings, concluded that Felty's syndrome and Still's disease were slightly different varieties of the same disease, both being manifestations of sepsis lenta usually from green-producing streptococci Features of the Still-Chauffard syndrome as described in European literature were summarized by Singer and Levy Williams noted the characteristics of the nine cases of "Felty's syndrome" so far reported The disease appeared in persons aged 45 to 65 years, of either sex Features were weight loss (average 40 pounds), intermittent moderate fever (99° to 101° F), chronic polyarthritis with repeated acute migratory exacerbations, roentgenograms showing "infectious arthritis" or mild indeterminate changes, splenomegaly (all nine cases), hepatomegaly (two of nine cases), pigmentation of skin (six of nine cases), slight general lymphadenopathy (five cases), leukopenia (800 to 4200 cells, av 2500), 14 per cent to 79 per cent (av 50 per cent) polymorphonuclears, 1 to 12 per cent eosinophiles, 14 per cent to 86 per cent (av 40 per cent) lymphocytes, occasional myelocytes (All of these features are often seen in cases of atrophic arthritis—Ed) In William's own case cultures of blood in life and of liver and spleen at death were negative, the patient died of pneumonia, lung cultures revealed green-producing streptococci Blood cultures in the cases of Singer and Levy revealed green-producing streptococci before death

(Further observations will be necessary before one can form a final opinion on the relationship between Still's disease and Felty's syndrome From data at hand we believe they are both varieties of atrophic arthritis That Felty's syndrome is a sepsis lenta does not appear to be proved Many chronic wasting illnesses terminate with a bacteremia of one sort or another—Ed)

Relation of Atrophic Arthritis to Other Diseases Possible relationships between atrophic arthritis and rheumatic fever, and tuberculosis and atrophic arthritis, were discussed under "rheumatic fever" and "tuberculous rheumatism"

Pathology With Deacon, Ghormley again stated that the focal collections of lymphocytes in synovia and adjacent bone marrow are the distinctive pathologic features of the disease. Present early and late, they bear no relationship to the duration of the disease. Contrary to the opinion of Fisher (1929) and of Jordon, the collections are not perivascular, as can be seen when tissues are stained with the Perdreau stain. Miller³⁶⁸ regarded the focal collections as "evidence that rheumatoid arthritis is an inflammatory disease of probable bacterial origin."

Roentgenographic Features These were discussed

Laboratory Data, Blood Counts A left-shift in the Schilling hemogram was noted by Cecil in 68 per cent of 28 cases, by Collins in 97 per cent of 59 cases. Unaffected by removal of foci, it was found even in cases of long duration. "The persistence of the shift lends support to the view that this disease is truly infective in nature and that the infection is not a transient phenomenon during the inception of the disease, which is often pyrexial, but continues as an infection capable of exerting its influence on the nuclear count for many years." Hartung, Davis, Steinbrocker and Straub found the nonfilament count elevated above 16 per cent (av count 30 per cent), in 96 of 100 cases of atrophic arthritis. Of 100 cases of hypertrophic arthritis the count was elevated in 53 (av count 22 per cent), normal in 47. "The high incidence of an elevated nonfilament count in atrophic arthritis suggests the presence of an infectious agent." A normal count indicates that atrophic arthritis is very likely not present.

Sedimentation Rates and Blood Proteins Davis noted the following sedimentation rates: 43 to 125 mm (1 hour) in eight severe cases, 15 to 80 mm in eleven moderately severe cases, 28 to 62 mm in five clinically arrested cases. The rate demonstrates roughly whether there has been a change in globulin or fibrinogen or both, provided correction is made for cell volume. Theoretically a diminished rate is not always an accurate index of improvement from vaccines, certain of which cause a rise in globulin which per se may increase the rate. Such was not the case with Davis' use of hemolytic streptococcus vaccine. In atrophic arthritis there was a rise in globulin, especially euglobulin, and in fibrinogen, a fall in albumin. These findings suggested to Davis that atrophic arthritis is an infectious disease.

The plasma cholesterol tends to be low in atrophic arthritis (high in hypertrophic arthritis). Serum calcium was normal^{130, 243}

Gastric Analysis Deficient gastric acid was present in 60 per cent of Collins' female and in 17 per cent of his male patients. It bore no relationship to the degree of left shift in nuclear counts. Fletcher noted gastric subacidity in 50 per cent of patients studied, many were anacid to alcohol, a few even to histamine. He estimated that anacidity is five times as frequent among arthritic patients as among normals. Histamine-refractory achlorhydria was found by Moltke and Ohlsen in 36 per cent of 30 cases of

atrophic arthritis The high incidence of achlorhydria was not accounted for by age or sex incidence "It possibly predisposes to the disease and may be a factor of much significance Perhaps it is an expression of an infective process of gastric mucosa which is responsible for the poor nutrition of the arthritic"

(How can achlorhydria be of primary significance when it is so inconsistently present? Gastritis has not been noted at necropsy in atrophic arthritis—Ed)

Synovial Fluid The cytology of 52 synovial fluids from 31 patients was noted by Collins to be as follows total nucleated cells, 5060 to 56,000 (av 20,170) per cu mm, differential count (in per cent) polymorphonuclears 41 to 95 (av 80), lymphocytes 3 to 45 (av 16), monocytes 1 to 14 (av 3), macrophages 0 to 3 (av 0.3), synovial cells 0 to 3 (av 0.4) The total protein per cent was 2.7 to 8.5 The polymorphonuclear count depends on three factors depth of the inflammatory process within synovial tissues, extent of synovia involved, type of inflammation present—acute, subacute or chronic

ETIOLOGY AND PATHOGENESIS OF ATROPHIC ARTHRITIS

Factor of Infection 1 Foci of Infection On the basis of the literature under review the pendulum could hardly swing farther away from the subject of foci of infection and keep it alive While many writers commented academically on the subject, less than a half dozen reported new investigations thereon Cultures of foci made in the usual way reveal more germs than those made by the pathogen-selective method (Solis-Cohen, 1927) but most of the bacteria thus isolated are of no significance, according to Murphy In the pathogen-selective method the patient's whole fresh blood may inhibit the growth of nonpathogenic bacteria, thus allowing the "specific" organism to grow out in pure culture Among 107 patients with "chronic arthritis" Murphy's results, by the usual and the special method respectively, were as follows positive cultures from nose in 100 per cent and 47 per cent from throat in 100 per cent and 79 per cent, from feces in 100 per cent and 24 per cent, from urine in 61 per cent and 34 per cent Bacteria recovered by both methods were streptococci and staphylococci the former more often from throats and feces, the latter from nose and urine

(Because of insufficient data no significance can be attached to these figures Although the four cases reported seem to have been of atrophic arthritis, no evidence was given as to the type of "chronic arthritis" present in the other cases No animal injections were made to support the contention that the bacteria isolated by the pathogen-selective method were more significant Their significance was assumed on the basis of results from vaccines—Ed)

An infected prostate is an important, often a more dangerous, focus than others because it so often escapes detection, according to Duncan Of

752 males with "chronic arthritis" who had prostatic examinations 41 per cent had definite prostatitis, 40 per cent had a history of gonorrhea. Prostatic foci were commoner than oral foci as the latter had often been removed.

(No bacteriologic work was reported. A clinical relationship was assumed on the basis of improvement in joints during prostatic therapy—Ed.)

Foci of infection of "etiologic importance" were present in 72 per cent of the cases of Davidson and Goldie, oftener in tonsils, throat and sinuses than in teeth. Asymptomatic colon bacilluria, noted in 8 of 24 cases, was considered of etiologic significance by Slot and Deville. In spite of such data, Joseph Miller concluded that there was no convincing clinical or experimental evidence that chronic foci of infection are responsible for atrophic arthritis. According to Fisher, the National Committee on Chronic Rheumatic Diseases of the Royal College of Physicians were of the opinion that the etiologic import of toxic foci is often exaggerated, although in some cases foci appear to be important, on the whole their significance has not yet been definitely established.

2 Blood Cultures Positive blood cultures were obtained by McEwen, Alexander and Bunim in 19 (54 per cent) of 35 cases: hemolytic streptococci in three, green streptococci in nine, indifferent streptococci in five, diphtheroids in three cases. Cultures were positive (for green-producing streptococci) in 5 per cent of 44 normal controls, in 25 per cent of senescent nonfebrile states. Therefore the streptococci recovered from the arthritic patients were considered unrelated to the disease. Without discussing their significance, Cecil stated that the bacteria isolated by him and by others were actually in the blood and not contaminants. Cultures of blood and joints made by Davidson and Goldie were "consistently negative" (no figures given).

3 Cultures of Joints The studies of Hadjopoulos and Burbank led them to propose the following hypothesis: If the cause of atrophic arthritis were a specific, immutable microorganism with stable immunogenic properties, the disease should resemble other acute infections and end by recovery if the system uses its defensive forces effectively, or by death if it is overwhelmed by extremely virulent invaders. But if the disease were due to a streptococcus capable of dissociating into microbic forms more resistant to the immune mechanism, the natural tendency of the host would be to encourage such a metamorphosis. At operation cultures were made from joints in 20 cases of atrophic arthritis: they were sterile in two inactive cases of arthritis, revealed diphtheroids in two slightly active cases, *Staphylococcus albus* or *aureus* and diphtheroids in eleven moderately active cases, streptococci in three active cases (green-producing in two, hemolytic in one). One patient with subacute tenosynovitis yielded *Micrococcus tetragenus* and sarcina, one with acute bacteremic arthritis yielded *Streptococcus hemolyticus*. One culture of hemolytic streptococci during a period of three months passed

through all these stages. It was concluded therefore that atrophic arthritis is caused by a multiple mutant infection—at first by a streptococcus which gradually changes into a diphtheroid, staphylococcus, or “*Micrococcus sarcina*” This may explain why sera of arthritic patients frequently react to a variety of apparently unrelated organisms

(This interesting work needs considerable repetition for its final acceptance—Ed)

4 *Agglutinins* It was reported again that most patients with atrophic arthritis possess agglutinins to hemolytic streptococci, generally in high titer, a few also possess agglutinins to green-producing streptococci usually in rather low titer (table 1). Agglutinins were not strain specific and tended to diminish eventually disappear, as recovery took place. Of 36 patients with active atrophic arthritis McEwen and colleagues noted agglutinins to hemolytic streptococci in 85 per cent, in a dilution of 1:20 in 6 per cent, 1:40 in 3 per cent, 1:80 in 20 per cent, 1:160 in 8 per cent, 1:320 in 6 per cent, 1:640 in 42 per cent. No agglutinins were present in three cases of inactive atrophic arthritis or in 35 normal controls. Hartung and his colleagues noted agglutinins to hemolytic streptococci in “significant dilutions” (1:160 or over) in 24 to 36 per cent of cases depending on the strain used, in only 10 per cent of controls, agglutinins to various strains of green-producing streptococci in 4 to 16 per cent of cases. Fewer agglutinins were present to hemolytic streptococci from fatal septicemia than to those of less virulent nature. Davidson and Goldie noted hemolytic streptococcal agglutinins in a titer of 1:200 in 75 per cent of cases of atrophic arthritis, in 5 per cent of controls. Figures reported by Goldie and Griffiths were agglutinins to hemolytic streptococci (titer 1:100 or over) in 89 per cent of patients with atrophic arthritis, in 71 per cent of those with nonstreptococcal diseases, in 10 per cent of controls, agglutinins to green-producing streptococci were present in dilutions 1:100 in only 5 to 7 per cent of arthritic patients and controls. In sera of 76 patients Dawson and Olmstead found agglutinins practically only to streptococci Lancefield group A, not to groups B to G.

5 *Precipitins* Strong precipitin reactions to C substance of hemolytic streptococci were observed by Dawson and Olmstead only in those sera which gave strongly positive agglutination reactions, that is, precipitation reactions in atrophic arthritis were characteristic only for group A hemolytic streptococci. The presence of common antigenic constituents produced a small number of cross reactions with extracts of other groups. Results of Chasis and McEwen were similar except for a greater number of cross reactions, the non-group-specific fraction present in bacteria and in the crude C-extracts responsible for these cross-reactions is not the nucleoprotein or P fraction, it is apparently nonprotein in nature. McEwen, Alexander and Bunim noted strong and frequent precipitations to group A streptococci not only in patients with atrophic arthritis, but also in those with rheumatic fever, with

known hemolytic streptococcal diseases and even in 24 per cent of normal controls. The test is therefore of no value in differential diagnosis.

6 *Antistreptolysins* (*Antihemolysins*, *Anhemolysins*) Dawson and Olmstead noted increased antistreptolysins in "early" cases of atrophic arthritis (less than one year's duration), particularly in those of acute or subacute onset, but not in most "late" cases (over one year's duration). The average value in 40 early cases was 125 units (in 26 it was 125 or more), that in 151 late cases was only 51 units, that in 91 controls was 62 units, only five controls having 125 units or more. McEwen and colleagues found increased antistreptolysins (over 150 units or more) in only 9 per cent of their cases of atrophic arthritis (in 3 per cent of normal controls, in 80 per cent of rheumatic fever patients). Longcope also noted distinctly lower antistreptolysin titers in atrophic arthritis than in rheumatic fever, of 55 arthritic patients 46 per cent had over 100 units, only 18 per cent had titers above 200 units. About 25 per cent of the patients of Goldie and Griffiths had 200 units or more, about 50 per cent had 100 + units.

7 *Antifibrinolysins* Sera of patients with atrophic arthritis contain some, but not as much, antifibrinolysin as that of patients with rheumatic fever. Of 11 arthritic patients, 36 per cent possessed "definite resistance," 18 per cent possessed "marked resistance," to fibrinolysis³⁸⁹. Similar resistance was noted in many normal controls. Stuart-Harris found much lower values for antifibrinolysins, none in 54 of 60 patients, partial resistance (that is, some antifibrinolytic activity) in 4, "complete resistance" (that is, marked concentration of antifibrinolysins) in only 2. Conclusions were that hemolytic streptococci were related to rheumatic fever but not to atrophic arthritis.

8 *Streptococcal Skin Reactions* Positive skin reactions to hemolytic streptococci were obtained by Goldie and Griffiths in 76 per cent (with a concentrated solution) and in 28 per cent (with a weaker solution) of their cases of "chronic infective arthritis", in 24 per cent and 0 per cent of controls. Positive skin reactions to green-producing streptococci were noted much less often, with a strong solution in only 11 per cent with a weaker solution in about 9 per cent of arthritic patients and controls.

Interpretation of Immunologic Data The presence of these antibodies (table 1) in patients with atrophic arthritis is strong presumptive evidence that hemolytic streptococci may play some rôle in the production of the disease. But if hemolytic streptococci are etiologically related to both rheumatic fever and atrophic arthritis it is difficult to explain the immunologic differences between them⁸³. Some of the reactions are sufficiently distinct to be useful in differential diagnosis. Agglutination and precipitin tests tend to parallel one another as do antistreptolysin and antifibrinolysin concentrations. Agglutination and precipitin reactions are strongly positive in atrophic arthritis, weak or absent in rheumatic fever, but antistreptolysins and antifibrinolysins are usually markedly present in rheumatic fever, absent

or weakly present in atrophic arthritis. Although agglutinins and precipitins are increased in atrophic arthritis they may be nonspecific antibodies, comparable to the Wassermann and Weil-Felix reactions (Myers). Some believe that the hemolytic streptococcal infection is of a different nature in the two diseases, the same agent producing a different response in each.¹³⁵ At present, obvious deficiencies in these tests exist, already discrepancies have appeared in the results of various workers. Until these difficulties are corrected, no final interpretation is possible.

Bacterial Allergy Although bacteria play a rôle, no one specific germ causes chronic arthritis, according to Holman, it is not the germ or germs alone, it is "largely a question of the time, the place and the germ." In spite of inconclusive skin tests with bacterial proteins, Young favored the theory of bacterial allergy. Ghormley and Deacon believe the disease to be related to bacteria even though the cellular reaction in synovia is not as one would expect from intra-articular bacteria. Perhaps the focal lymphocyte collections in synovia represent an allergic response to some bacterial or other toxin. Miller believed it impossible to explain the pathologic process on an allergic basis. Myers regarded the theory inadequately supported and unproved.

Virus Theory Although this theory seemed attractive to some,²²⁸ no further data in support of it were reported.

Factor of Circulatory Disturbance No new data on circulatory disturbances as a cause of atrophic arthritis were presented. The primary importance of such a factor seemed unproved to Myers. Histologic examination of affected synovia reveals, not vasoconstriction but a large blood supply and many open capillaries. Atrophic arthritis is a rare complication of thromboangitis obliterans, arteriosclerotic occlusion, Raynaud's disease or scleroderma.

Factor of Altered Metabolism, Carbohydrate Forbes and his colleagues considered the effect of a high carbohydrate diet harmful. But when Bowen and Lockie gave high carbohydrate (425 to 500 gm.) high calorie (2200 to 2700) diets daily for 15 to 65 weeks to eight patients with advanced atrophic arthritis no exacerbations were produced. By this diet arthritis was made neither worse nor better, but weight gains and improvement in skin texture and general nutrition were noted. The sugar tolerance of 49 arthritic patients (23 with atrophic, 15 with hypertrophic, 11 with mixed, arthritis) was tested by Peers, using the old routine test which showed delayed removal of sugar in 83 per cent, and by the new Exter-Rose test which showed abnormal curves in 57 per cent of cases. Peers concluded that the older test was more accurate and that the abnormal sugar curves reflect a constitutional disturbance of secondary, not etiologic, import. According to Myers many studies on sugar tolerance curves have been "unconvincing," done without due regard to certain factors (patient's age, nutrition, amount of sugar actually absorbed, and so forth). Carbohydrate indigestion is not

limited to arthritic patients, and when present, usually follows rather than precedes arthritis

Calcium Wootton vaguely referred to atrophic and hypertrophic arthritis as "end results of serum-calcium vagaries" No supporting data were given

Sulfur Metabolism and Hepatic Dysfunction According to Forbes and his coworkers indoluria is usually present in "chronic arthritis" (and other conditions), generally parallels the activity of the disease and disappears when joints markedly improve Indole may arise from foci of infection, or, when these are absent, possibly from intestinal decomposition of tryptophane, indole being either formed in abnormal amounts or allowed to pass through the liver not detoxified Sulfur is necessary for its detoxification and conversion into indican (potassium indoxyl sulfate) Indoluria may indicate impairment of hepatic detoxification resulting from a sulfur deficiency in the liver Reputedly the sulfur content of articular cartilage and of fingernails is low in arthritis Forbes and his colleagues produced "typical arthritic changes" in joints of rabbits by the intra-articular injection of small amounts of indole

(Many substances will produce them—Ed)

Perhaps indole, passing undetoxified through the liver with other toxic substances which gain similar entrance, is a contributing factor in chronic arthritis On the basis of this hypothesis high sulfur-low carbohydrate diets were given 22 patients with atrophic arthritis and to eight with hypertrophic arthritis, most of whom had indoluria Twenty of the former and five of the latter "improved markedly" Coincident with improvement, indoluria ceased Some patients whose diets were interrupted noted return of joint pains Since the diet was low in carbohydrate and rich in sulfur and vitamin B it was admittedly impossible to ascribe relief to the sulfur alone

Vitamin Deficiency Deficiency in vitamin B, C or D has been regarded as an associated factor in the production of chronic arthritis of either type Fletcher has suspected a latent deficiency in vitamin B Recently Rinehart and his coworkers attempted to establish vitamin C deficiency as an etiologic factor in both atrophic arthritis and rheumatic fever The basis for this idea was noted previously²⁴⁷ and was restated According to Rinehart, vitamin C deficiency in guinea-pigs produced a painful deforming arthropathy resembling atrophic arthritis—synovial proliferation, pannus formation and periarticular fibrous thickening Superimposed infection sometimes accelerated and accentuated these pathologic processes which included changes in bone, muscle and skin Normal plasma values for ascorbic acid are 0.7 to 0.9 mg per cent, levels below 0.7 mg per cent are suboptimal, those below 0.5 mg per cent are low (Rinehart, Greenberg, Baker) Low values (0.14 to 0.66 mg per cent) were noted in 21 patients with atrophic arthritis on their usual diet High values (0.90 to 1.39 mg per cent) were noted in 12 arthritic patients given an intake rich in vitamin C (Six pa-

tients with hypertrophic arthritis had normal or high values—0.90 to 1.34 mg per cent) Although low levels of plasma ascorbic acid are not peculiar to atrophic arthritis and in a given case do not indicate the existence of scurvy, these consistently low values in arthritis seem significant. The mechanism involved is unexplained.

(In this connection, and apropos of Hench's observation (1933) that notable jaundice temporarily "inactivates" atrophic arthritis and fibrositis, the observation of Sendroy and Schulz is of interest: jaundice seems to increase urinary excretion of ascorbic acid. "In cases of icterus, the abnormal titration of the urine may be caused either by the increased excretion of reducing substances other than ascorbic acid, or by a real disturbance in the ascorbic acid excretion or utilization process"—Ed.)

Because several patients with atrophic or hypertrophic arthritis improved while on concentrated vitamin D, Livingston assumed that arthritis is associated in part with a vitamin D deficiency.

Food Allergy and Dietary Habits Young noted that patients with atrophic arthritis are apparently abnormally susceptible to skin allergy (urticaria and allergic dermatitis) but not to hay fever or asthma. Hay fever or asthma or both were present in 15 per cent of 200 arthritic patients, in 14 per cent of 50 controls. Skin allergy was present in 32 per cent of arthritic patients, in 12 per cent of controls. However, only 4 per cent of 50 patients with allergic dermatitis and 2 per cent of 50 patients with urticaria had arthritis. In spite of the susceptibility of arthritics to skin allergy, skin reactions to food or bacterial proteins in 20 patients were of little value. Even in cases in which a known food sensitization was present, articular symptoms were not aggravated by ingestion of foods to which patients were clinically sensitive. Fifteen arthritic patients with skin allergy from known foods were fed the irritating food repeatedly, at no time was the arthritis affected. Young's results therefore do not support the idea that arthritis is caused by dietary disturbance or food allergy.

(A case of allergic synovitis presumably due to English walnuts was reported by Lewin and Taub and will be noted later.—Ed.)

Intestinal Toxicosis "Though there is not sufficient laboratory or clinical evidence to show that [atrophic] arthritis is a definite disease due to errors in metabolism, clinically I believe that the primary form is metabolic and probably due to some imbalance in endocrines" (Pringle). Thus many writers vaguely blamed the disease on abnormal metabolic processes involving intestinal dysfunction, and endocrine imbalance. Others objected to the vagueness of the terms "imbalance," "dysfunction" and "metabolic error," and asked how they operate to produce arthritis. To them gastric anacidity, colonic abnormalities and carbohydrate indigestion, inconsistently present, are not the cause of arthritis but the result of prolonged illness.²²² Current literature included no further data.

Endocrine Abnormalities With no support whatever one writer²²⁰ in-

criminated practically all the endocrine glands by name in atrophic or hypertrophic arthritis. In atrophic arthritis "usually the metabolic rate is below average and sometimes well below the limits of normal" (Fletcher). Statements such as this are not uncommon^{52, 531} and have been challenged by those who generally find normal rates. Peers noted metabolic rates below minus 9 in 14 of 39 cases of atrophic, in 17 of 28 cases of hypertrophic, and in 7 of 12 cases of "mixed" arthritis. But he concluded that "the true arthritic is a non-myxedematous individual". Low rates were not due to lack of thyroid hormone but were brought about in some other fashion and are merely another reflection of a constitutional disease.

(Certain of these low rates may be normal for the individual—Ed.)

Disturbance of the Sympathetic Nervous System No new data on this point were reported except the observation that sympathectomy provides relief to certain arthritic patients⁵⁹¹. But because sympathectomy does not completely arrest the disease consistently and because many arthritic patients do not have vasomotor disturbances even or until late in the disease, Myers concluded that the vasomotor phenomena, although they aggravate symptoms, are incidental and that a disturbance of the sympathetic nervous system is not the cause of arthritis.

(Obviously the cause of the disease is unknown. The editors of these reviews have been mildly criticized for not making a stronger case for the metabolic or endocrine theories, for "playing down" papers supporting these ideas. Regardless of our individual convictions we have tried to review all papers fairly, to "take them as they come". Indeed an admitted fault, perhaps a serious one, is that in our efforts to be impartial, repertorial rather than too judicial, and to give new or contentious ideas a hearing, we have been too inclusive, not exclusive enough, and have reported much inferior work herein. Paraphrasing the automobile advertisement when better and more papers on the metabolic and endocrine theories are available, the review will welcome them. Unfortunately in the absence of much concrete evidence in favor of these theories, papers thereon have been as a rule most speculative, hypothetical and philosophical. Although unproved, the infectious theory remains dominant by the content as well as by the volume of literature thereon. However, there seems to be a current reduction in the number of papers thereon and in the zeal of their authors. Investigations on foci and blood cultures have become momentarily less popular and interest has swung to the immunologic reactions involved. These are difficult to interpret. Indirect evidence is so much less satisfactory than direct evidence that some, confused by the uncertainty and contradictions thereof, are inclined to favor the infectious theory in spite of rather than because of, all the bacteriologic and immunologic data so far presented. The importance of beta hemolytic streptococci in the etiology of rheumatic fever and atrophic arthritis should be somewhat deflated if it is shown (as preliminary and unpublished reports seem to indicate it will be shown) that sulfanilamide, so effective in diseases of known hemolytic streptococcal origin, is of little or no value in rheumatism. If so one cannot escape the conclusion that such streptococci play a minor, not a primary rôle, or no rôle at all, in which case the antibody reactions thereto must be nonspecific—Ed.)

TREATMENT OF ATROPHIC ARTHRITIS

General Remarks Atrophic arthritis is a generalized disease requiring individualized treatment. A systemic disease, "it is no more a disease of joints than typhoid fever is a disease of Peyer's patches" (Pemberton). No single form of treatment is adequate. Lacking a specific remedy, physicians have too often, like the children of Israel, wandered afar after strange gods.²⁶⁹ Although some studies on therapy have been well controlled and have taken into consideration the natural history of arthritis and its tendency to spontaneous remissions, too many have consisted of uncritical observations of a few patients for a short time only and are of little or no value. The aggressive doubter will insist that the control method be used. "I could almost cry when I read of one case cured by drug X, knowing so well the vagaries of the disease even when untreated," so wrote one physician.⁴³⁸ In evaluating treatment one must rely most on objective improvement, less on the patient's subjective relief. Otherwise, one will be misled by the psychic effects inherent in any measure. "An enthusiastic physician may acquire at least a temporary reputation for great skill."³⁶⁸ Nevertheless, enthusiasm and optimism are essential, if the physician exhibits a lack of therapeutic resources his patient will catch the air of futility with resultant serious depression. In appraising the value of favorite remedies one must remember that "experts also are liable to fashions." One should not be mesmerized by a spa, a local focus, a diet, a drug, a vaccine, short-wave therapy or physiotherapy, neither should one be foolish enough to decry them.⁴³⁸ Among the pitfalls in a study of therapy is that of the dangerous but helpful drug: its full effects must be studied so carefully, for what seems to be a dangerous drug today (e.g. gold) may be improved by further knowledge. These were a few of the useful generalizations currently expressed.^{5J, 269, 279, 368, 438, 439}

Management of Foci of Infection Many regarded elimination of foci of infection the measure of first importance.²⁷⁹ Abhorring the promiscuous removal of foci one should nevertheless insist on the radical removal of any suspicious infection.⁶⁹ One physician wrote sternly, "When an individual refuses to have definite foci removed, they are informed that both disease and cause are theirs to do with as they choose and are requested to seek advice elsewhere." Foci should be removed early in the disease, but Pemberton, Phillips, Holbrook and Hill considered it often necessary to raise the patient's resistance beforehand, this was done by a preoperative transfusion and periods of rest and weight-gain. Buckley sometimes noted "most remarkable improvement, even a cure" from removal of foci, occasionally a temporary exacerbation occurred.^{79, 531} Others were not so convinced of the value of removal of foci. Miller found the reports of favorable results therefrom unconvincing. Too often removal of foci was included with other therapy, thus clouding the issue, and the value of removal of foci is too often casually assayed on the basis of letters from patients. Miller considered it unfortunate that the removal of chronic foci is consid-

eried by so many to be the first and major treatment " This procedure has been responsible for the loss of much valuable time which might have been utilized more profitably in other directions " Fletcher suggested that some foci of infection may be merely an expression of poor health, not the cause of it, therefore arthritic patients may develop new foci during their disease The fact that the removal of foci of infection is not followed by rapid or notable relief does not, however, invalidate the importance of their eradication Several ^{59, 129, 569} insisted that results from removal of foci may be poor because often more than one focus is present, foci are too often imperfectly removed, indeed it is practically impossible to eradicate them completely as many " foci " are not local but diffuse (for example, nasopharyngitis), and joints themselves may be foci Lastly too much is expected of removal of foci in the presence of irreparable articular pathologic change

As in other things, there are fashions in foci and the literature mirrors these changing fashions Many who advocate eradication of foci will one year pounce on the prostate, another year on sinuses and so on One physician " had yet to see a case of arthritis from sinuses, gall-bladder, colon or prostate ", his own favorite focal enemy was situated elsewhere

Teeth No more than two infected teeth should be removed at a time (O'Brien) Only infected teeth should be removed, too often the wholesale removal of teeth to " clean up the mouth " causes serious nutritional difficulties for the edentulous patient

Tonsils These came in for very little notice

Sinuses Littell stressed the frequency of " silent sinusitis " especially in ethmoids Surgical treatment of sinusitis was applied in 20 cases of atrophic arthritis, 2 patients were unimproved, 3 slightly improved, 15 markedly improved

(Surgical operations on symptomless sinuses should be done only after much deliberation and when done their effects should be most cautiously appraised Only the most carefully controlled observations can determine whether or how often such a procedure is justified —Ed)

The importance and frequency of the *nasopharynx*,⁵² *cervix*¹⁶⁴ and *prostate*¹⁵⁵ as foci of infection were stressed One writer⁵⁴⁶ regarded the *gall-bladder* as a focus infected more often than suspected " Removal of bile through a duodenal tube may show that the gall-bladder is a carrier of streptococci, although the patient has no definite symptoms of cholecystitis "

(The isolation of streptococci from a duodenal tube after so-called duodenal drainage is not sufficient evidence to consider the gall-bladder infected Recent statistics^{245, 247} indicated the rarity of cholecystitis as a focus in atrophic arthritis and the rather unimpressive effects of cholecystectomy in this disease, even when markedly infected gall-bladders were removed —Ed)

Blake reported the case of a woman with epilepsy and atrophic arthritis of seven years' duration, spectacular recovery from both arthritis and epilepsy followed an appendectomy for acute *appendicitis*

(It is difficult to believe that the appendix was a focus here or that appendectomy had a specific effect. Similarly dramatic effects not infrequently result after any surgical operation from the effects of the anesthetic, the operation and hospital rest and regimen—Ed.)

Vaccines From the standpoint of literature this was not a very good year for the cause of vaccines. Wyatt, Hicks and Thompson administered to 240 patients with atrophic arthritis intravenous injections of an antigen from nonhemolytic streptococci. A marked or definite improvement was noted in 85 per cent, increased agglutinins in 80 per cent. Sedimentation rates were favorably affected. It was admitted that other forms of treatment were coincidentally applied and that no control series was set up. Davidson and Goldie gave very small doses of hemolytic streptococcal vaccine intravenously "with apparently successful results in some cases." No other data were given. "Fairly encouraging results" were noted by Lecklitner who used Crowe's *Micrococcus deformans* and polyvalent streptococcus vaccine in conjunction with other measures. Autogenous vaccines made especially from nasopharyngeal bacteria to which skin sensitivity was evident were used by Breuer. The "most amazing and apparently ridiculously small" doses were used. 100,000 or even 1000 bacteria might give no relief or even make the patient worse, but the use of 100 or even 50 bacteria "will produce remarkable results in a few hours." Using "specific autogenous vaccines" of streptococci or staphylococci or both cultured from various foci by the pathogen-selective method, Murphy noted relief in some cases even when staphylococci were used alone. Greer treated 50 cases of atrophic arthritis with "very small doses" of autogenous vaccine alone or autogenous and Crowe's vaccine given intravenously. A total of 88 per cent were improved. He considered the intravenous route superior to the subcutaneous one, since only 55 per cent of a former series of patients treated subcutaneously were benefited.

(The fact that in 15 of the 50 patients only one joint was affected makes one wonder how many of the cases were of atrophic arthritis—Ed.)

Some patients with persistent arthritis who were hypersensitive to streptococcal vaccine were found by Hitchcock to have staphylococcal sinusitis and to be hypersensitive to staphylococcal vaccine also. In 9 of 16 such patients the arthritis was benefited by the alternating use of staphylococcal toxoid and vaccine.

Comparing the results from different vaccines variously administered, against a control series, Holbrook and Hill were unable to prove vaccines of definite value. Nevertheless they continued to use them in some cases because of the clinical impression that certain cases were helped. With others they condemned the indiscriminate use of vaccine as a "specific remedy" to the neglect of other therapy. Doubtless many patients are somewhat benefited, but as Irons put it, vaccines are too often used as a sort of "occupational therapy" by the patient and the physician anxious for "some-

thing to do" Much of the previous work on vaccines was criticized by Kovacs because there were no controls, no routine assay of the activity of the disease was made or noted, sometimes the courses of vaccine were so long that spontaneous remissions could have occurred, usually additional therapy was given Reports on vaccines have been given by (1) those who noted excellent results in either atrophic or hypertrophic arthritis, (2) those who noted some results but only in atrophic arthritis and in conjunction with other therapy, and (3) those who noted no better results from vaccine than from other measures Kovacs gave various vaccines to 100 patients with "chronic arthritis" Although 30 to 40 per cent of each group noted some relief, controls treated by saline injections were similarly relieved

According to Buckley,⁵⁹ vaccines often do more harm than good Desensitization, not immunization, should be attempted, reactions should be avoided Best results were from progressively *smaller*, not larger, doses Others considered them "of doubtful value," "not routinely justified" ^{181, 431, 433, 546, 548} Holman expressed his opinion of them as a bacteriologist Nobody knows how they work, not even their most enthusiastic advocates It is impossible to evaluate them but there is little or no evidence that they are "specific" Using them, we are treading on uncertain ground "When we think we are immunizing, we may be desensitizing, and when immunity peters out we may then have an unexpected sensitization We are playing with a dangerous weapon in a confused field If I had arthritis, I might—but I doubt it—run the risk of interfering with the little understood balance of sensitivity and immunity by the use of vaccines or other suitable antigens if I were at all sure which were the responsible microorganisms in my case"

(It is difficult for a physician or layman without arthritis to say what he might or might not do were he to develop progressive atrophic arthritis Methods of treatment which seem quite unjustified, even risky, to the unaffected, frequently will be welcomed enthusiastically or endured philosophically by the sorry victims of this disease Although the patient's willingness to try anything does not release his physician from the necessity of adopting a critical and judicious attitude on any therapy proposed, the stubborn nature of the disease gives the harassed physician the right in individual cases to institute cautiously such therapy as vaccines, provided both the physician and the patient appreciate the difficulties involved and exercise care to avoid harmful reactions—Ed)

Foreign Protein Reviewing an experience of 20 years with triple typhoid vaccine injections, Miller noted that about 40 per cent of patients so treated had been entirely relieved from pain and tenderness after receiving three to five injections given once every other day Within a month, 50 per cent (of the 40 per cent) had a return of their disease Most of the remainder had a return of the disease after several months, perhaps a year A few had no recurrences in five to ten years The earlier in the disease they are given, the better the results

Venom Therapy Of patients treated by Mackenna with bee venom

("apicur") many were benefited, but since other treatments were given coincidentally it was impossible to say what caused the improvement. Beck noted "surprisingly successful results" in the treatment of an unstated number of patients with "arthritic and rheumatoid ailments" with bee venom, the hemorrhagic effect of which presumably produced an increased tissue oxidation. No physiologic or clinical data on cases treated were given. A 75 year old woman with chronic "hypertrophic" polyarthritis developed a severe allergic reaction from the sting of a wasp. Six weeks later she reported to Lincoln that her arthritis had been improved greatly since the wasp sting. She had not been so agile in years and was practically free from pain. The effect persisted for four months, then crippling returned.

Diets Although the arthritic patient still wants a special diet, the disease usually does not need one, that is the current opinion of most rheumatologists. Less is being written in favor of restrictive diets and special food combinations. As Swain said, until we know more about the disease we must be rational about diets for it. "The patient does best on that diet which would be selected for him if he had no arthritis" (Holbrook and Hill). If the patient is underweight these authors prescribe a high-calorie high-vitamin diet with no limitation of starches. Later, a high-vitamin weight-maintenance diet, low in starch, is given "not because starch is harmful but the starch eater will seldom eat enough food containing vitamins and minerals." The majority^{59, 279, 548} prescribed a high-calorie, high-vitamin diet except for the obese. A daily minimum of 50 to 75 gm of protein should be taken.¹⁸¹ Others^{222, 431} still curtail carbohydrates, but Bowen and Lockie noted no harmful effect from diets rich in carbohydrates (420 to 500 gm daily) given to 8 patients with atrophic arthritis for 15 to 65 weeks. Joints were neither worse nor better, but general nutrition was improved. On empiric grounds, Hare prescribed a raw vegetable diet to four patients with atrophic arthritis. Only raw foods were given for two weeks, then cooked foods were added. Two patients were not improved, two improved somewhat for five weeks. Sedimentation rates were unaltered. Relief obtained was ascribed to the diet's low sodium content producing marked fluid loss.

(No laboratory or clinical data to prove this were included—Ed.)

For reasons noted, Forbes and coworkers prescribed a high-sulfur low-carbohydrate diet. 20 of 22 patients were "markedly improved", two were not improved.

Additional Intestinal Therapy The general principles of gastrointestinal hygiene for arthritics were noted by Pemberton, Fletcher, and others. For those with achlorhydria, hydrochloric acid was prescribed.^{181, 546} Salol was used by some. Colonic irrigations were considered useful by some,¹⁰⁷ of no value by others.²⁶⁹ Adequate elimination is best promoted by proper

diet, abdominal exercises, massage, habit-time and not by cathartics. Breuer permitted small doses of magnesium sulphate before breakfast.

Vitamins Various vitamins were prescribed by those who regard vitamin deficiency as a contributing or predisposing factor. Vitamin A, generally as cod liver oil, was considered most useful, especially in winter.^{50, 181} Vitamin B, in brewer's yeast or wheat germ, was advocated by others.^{181, 269} Live yeast should be avoided, a few cases of toruliasis therefrom have been reported.⁵² Fletcher used generous amounts of orange juice and grapefruit juice to supply vitamin C, but no striking benefit accrued to a group of patients to whom Holbrook and Hill gave intravenous injections (150 mg) of crystalline vitamin C three times a week for several months.

After the method of Dreyer and Reed (1935) massive daily doses (150,000 to 250,000 U S P X units) of vitamin D (concentrated viosterol) were given by Vrtiak and Lang to 20 patients for 1 to 12 (av 3) months. Two patients showed marked, six moderate, four slight and eight no improvement. Results were not unlike those from other methods of treatment. Undernourished and anemic patients improved least. Roentgenograms in five cases before and after treatment gave no change in bone density. Signs of toxicity developed: nausea in all, frequency of urination and nocturia in a few. The series of cases was too small for an evaluation of vitamin D "but is sufficient to indicate [the need for a] conservative attitude" toward it. Vitamin D concentrate (Ertron) in daily doses of 200,000 to 600,000 U S P or International units was given by Livingston, alone to five patients, with fever therapy to nine other patients. Improvement was noted by four of the first, eight of the second group. Fever therapy plus vitamin D seemed to cause more rapid improvement than either alone. Toxicity was noted frequently, nausea, urinary frequency, lassitude, anorexia, polydipsia, diarrhea, severe gastrointestinal pain and vomiting. When toxic symptoms appear, administration of the drug should be discontinued at once for one to two weeks. Brewer's yeast was ineffective in preventing or ameliorating toxicity. In some cases improvement was not noted for from one to three months. Medication was continued indefinitely until maximal benefit was noted. Blood and urine calcium and phosphorus were unchanged. There was a right shift in Schilling hemograms, a decrease in sedimentation rates. Holbrook and Hill gave 200,000 to 350,000 units daily for four months to 25 patients. In five there was less pain, in four a marked drop in sedimentation rates. Irons expressed doubts as to the wisdom of giving vitamins in large doses to cure arthritis. "Neither is an immediate favorable effect on joints clearly proved, nor have the more remote and possibly unfavorable effects of massive doses of vitamin-concentrates on human tissues been determined."

Chronic hypercalcemia was produced by Fang and Miltner in albino rats by prolonged (six or more weeks) administration of large doses (2 to 5 mg daily) of irradiated ergosterol. Those on 2 mg daily showed weight gain

and no pathologic change. Those on larger doses developed marked skeletal decalcification with early cystic changes, metastatic calcification in heart and various blood vessels, and calcification of extra-articular collateral vessels of knee joints. Cartilage of knee joints and of intervertebral disks showed areas of degeneration and calcification—changes not unlike those of early human degenerative arthritis. There were no histologic changes produced in parathyroids to support the contention that vitamin D acts through them. Some of the rats which had developed hypervitaminosis were put back on a normal regimen, their tissues examined later. No histologic changes were visible, indicating that rats may recover completely from the effects of prolonged feeding of vitamin D within two to three weeks after the drug is withdrawn. Large doses of vitamin D produce a marked calorogenic action in normal dogs and rats. In thyroparathyroidectomized dogs, however, such doses produced no marked augmentation in metabolic rates, therefore Deutsch, Reed and Struck concluded that the thyrotropic effect does not concern parathyroids.

(Two of us, C. H. S. and P. S. H., have given 250,000 to 600,000 U. S. P. units of concentrated vitamin D to about 25 patients with atrophic arthritis, the drug being given daily (except for occasional short interruptions) for one to two years. Cures were not obtained, articular lesions were generally altered but little, but some of the patients noted reduction in pain and soreness and increased well being. Toxicity was frequently encountered and was inadequately controlled by brewer's yeast. Two instructed patients carelessly ignored signs of early toxicity and continued use of the drug one to three weeks longer. Their severe headache, anorexia, vomiting, weight loss, transient uremia and hypercalcemia promptly disappeared under appropriate treatment. When smaller doses were used toxicity did not appear.—Ed.)

Transfusions Holbrook and Hill regarded transfusions as a valuable adjunct in treatment. In chronic cases no results were noted. In acute and subacute febrile cases, "good, sometimes dramatic results" were obtained, fever and swelling subsiding. The first two transfusions were given a week apart, later ones as necessary.

(It is particularly difficult to evaluate measures used in acute and subacute cases because more or less rapid diminution in inflammation is almost inevitable regardless of what is used besides rest and physiotherapy which the patient's joints generally demand.—Ed.)

Medicines, Miscellaneous Substances Intragluteal injections of leukocyte concentrate were given by Hartung and Straub to ten patients for 3 to 40 weeks. None were cured, six noted symptomatic improvement. Blood counts and sedimentation rates were unaltered.

Insulin provides a "metabolic fillip" of value in debilitated cases with weight loss and anemia.^{164, 222} Ellman used 5 units daily the first week, an additional 5 daily units each week to a maximum of 30 units daily (15 units B. I. D.). Insulin was given 20 minutes before the principal meal, which was followed in 3 hours by glucose or a glass of milk to avoid hypoglycemia.

The trend is away from drugs since most of them have not justified

themselves²⁷⁹ The fashion has now changed from arsenic and iodides to gold and sulfur, Fletcher doubted whether the change represented an advance Gutman listed scores of commercial preparations and their supposed indications Thyroid in small doses was prescribed for those with low metabolic rates as incidental, not as specific therapy^{52, 181, 548} Cinchophen was considered a useful, reasonably safe analgesic by some⁵⁰³ Rawls considered the use of amidopyrine safe in young arthritics, unsafe in patients with long standing atrophic arthritis or in elderly patients with hypertrophic arthritis Of 400 patients with different diseases who received variable amounts of the drug, four (1 per cent) developed agranulocytosis of whom three died Two had long standing atrophic arthritis, two had hypertrophic arthritis A study of the effect of prolonged doses of the drug on 100 arthritic patients (44 with atrophic, 66 with miscellaneous arthritides) was made, none developed agranulocytosis or apparent changes in leukocyte count Breuer regarded amiodoxyl (ammonium-iodoxy-benzoate) "merely a fad which has just about passed out" Unfortunately, at least, six patients passed out with it, case reports of their deaths were collected by Hamilton whose results with it were "so poor that it has been long since discontinued" Macht and Mayo recommended bromsalizol (mono-brom-saligenin) as a superior analgesic Quick relief of pain results from the use of rhodan-calcium-diuretin, according to Zaki The Ru-Mari arthritis cure was exposed as an alkaline nostrum⁶²

Sulfur Having found colloidal sulfur and such sulfur-containing substances as contramine and iodolysin of no value Krestin gave "sulfosin" (1 per cent suspension of sulfur in oil) intramuscularly every five to six days Febrile reactions were induced in 40 patients with varying degrees of bony change "good results" (no symptoms, normal motion) were noted in 18, "considerable recovery" in nine, partial recovery in eight, no improvement in five Relapses within 4 to 24 months appeared in 25 per cent "Recurrence is not surprising, since there is no reason to believe that intramuscular sulphur affects the cause" It should not be given in the acute phase (exacerbations resulted), to elderly, feeble, or emaciated patients, to nervous, hysterical patients, to the very obese (they don't stand it well), or to those with tuberculosis or other "active organic disease"

(The cases were not well classified Some patients were hospitalized with bed rest No control group was studied Relief may have resulted from febrile reactions—Ed)

Ellman also recommended "sulfosin" reactions Breuer's results (not given) with colloidal sulfur given intravenously were "favorable in a small number of cases" Results of Holbrook and Hill with "sulfur injections" were "disappointing"

Gates considered sulfur "a forgotten remedy" worthy of reinvestigation "I have given sulfur in [arthritis, etc] when there was no indicanuria After giving it there was an abundance of indicanuria and the patient was

greatly relieved" The presumed virtues of a diet rich in sulfur were noted by Forbes and associates Miller concluded that no report to date contained suitable controls or careful objective studies of reputed improvement Periods of treatment were long enough for spontaneous remissions to appear

Gold Salts The treatment of arthritis by gold salts was instituted about 10 years ago British writers now speak of it as "very valuable" (Slot), "a therapeutic measure of the first order" (Baker), "the most important form of treatment for arthritis" (Hartfall and Garland) According to Tegner "It has always been regarded as unfortunate in Europe that the claims of chrysotherapy in the treatment of certain types of chronic arthritis have been virtually disregarded in America" If claims made for it are true, we probably deserve this chiding because until now no formal American report on the value of gold has appeared

The mode of action of gold in arthritis is unknown Intramuscular injections of gold are easier and as effective as intravenous injections²⁴⁰, oral administration seems ineffective¹⁴ Most workers now confine its use to atrophic arthritis Bach considered it useful in any "rheumatoid type of arthritis" with proliferative synovial reactions including gonorrheal and tuberculous arthritis It is said to be equally effective at any stage of atrophic arthritis but of limited value in spondylitis ankylopoietica^{14, 18} (In hypertrophic arthritis it is somewhat useful according to some,⁴⁹⁸ useless according to others^{14, 18, 59} It is said to be useless in rheumatic fever, muscular rheumatism and gout)

The drug is given in courses with free periods between, much as in the chemotherapy of syphilis Injections are given every few days, initial doses varying from 0.05 to 0.1 gm, the dose usually being gradually increased Differences of opinion exist on what constitutes one course it was variously limited to a total dose of 1 gm (Hartfall and Garland), 1.0 to 1.5 gm (Buckley), 1.2 gm (Slot), 1.5 gm (Phillips), 1.8 to 2.4 gm (Williams), 2 gm (Baker), 2.5 gm (Bach) Copeman's course for children totalled 0.25 to 0.50 gm Rest periods between courses varied four to eight weeks¹⁴, two to three months⁵⁹, three plus months²⁴⁰, six months¹⁸ The number of courses necessary for results varies, the majority believed that at least two courses were necessary and that many failures or relapses resulted because subsequent courses were not given Bach gave courses intermittently for 6 to 24 months

The management of such therapy includes frequent analyses of urine, blood counts and sedimentation rates to gauge progress and dosage and to avoid reactions if possible If after six to eight weeks of injections the sedimentation rate is not falling, a larger dose or a new preparation should be used, or one should stop the therapy¹⁴ Progress is slow, results may not be noted until after 8 to 12 injections Various gold salts were used allochrysine, sanocrysin, solganol B oleosum, myochrysine, myoral, crisalbine, lopion

Reactions were numerous, some incidental, others more serious, some fatal. Reactions at the site of injection were usually avoided by local massage. Focal reactions, joint pains for several hours, occurred in 5 per cent of Bach's cases. General reactions—fever, increased joint pains—occasionally occur, in which case the dose should not be increased. Toxic reactions were uncommon according to some, unfortunately common according to others, "considerably more common than most of us care to admit" (Crosby). They involve many tissues. Skin was commonly affected (in 5 to 10 per cent of cases¹¹), with erythema, exanthema, papular eruption, desquamation, soreness, morbilliform rashes, urticaria, and occasionally serious exfoliative dermatitis, cases of which were seen^{11, 123, 240, 275}. If skin reactions were local, courses were not interrupted, if general, treatment was interrupted¹⁴. Other tissues frequently affected were eyes (conjunctivitis), mouth (metallic taste, anesthesia of tongue, transient loss of taste, dysphagia, sore tongue and gums, ulcerative stomatitis), gastrointestinal tract (weight loss, nausea, vomiting, epigastric distress, diarrhea, rarely rectal spasm), liver (hepatitis, jaundice, rarely acute yellow atrophy),⁴⁹⁸ respiratory tract (cough, "gold bronchitis"), kidneys (generally mild, transient albuminuria, occasional uremia), central nervous system (one case of persistent eighth nerve deafness¹⁴), hematopoietic system (epistaxis, purpura hemorrhagica, aplastic anemia, agranulocytosis). While affections of other tissues may be serious, those of the hematopoietic system are most serious, occasionally fatal. Serious agranulocytosis and fatal purpura hemorrhagica were noted by Bach, fatal aplastic anemia by Hartfall and Garland. Additional toxic symptoms were headache, dizziness, tinnitus, sleepiness, fever, general malaise⁴³². When administered intravenously (which is not necessary) shock and pulmonary edema have been noted⁴⁹⁸.

Careful investigations of these toxic manifestations were made, notably by Hartfall and Garland, and by Crosby, reactions being analyzed in relation to many factors, individual and total dose, type of salt used, age and condition of patients and so forth. Williams and Bach believed that much toxicity could be avoided by the coincident injections of calcium gluconate but Crosby doubted its efficiency, and Hartfall and Garland noted no significant reduction of toxic manifestations. Others believed risks could be lessened by use of liver extract or glucose. Patients were warned to complain of any unusual sign or symptom. If eosinophilia of 7 to 8 per cent or more was noted, smaller doses were given¹⁹⁸. Contraindications to such therapy were arthritis with acute or chronic nephritis (since 75 to 80 per cent of the gold is excreted by kidneys, the rest by stools), diabetes, congestive heart failure, blood dyscrasias, hepatic insufficiency, possible contraindications were marked debility and hypertension. According to some, hypertension, age and arteriosclerosis are no contraindication^{18, 240}.

(Original papers should be consulted regarding prevention, amelioration and treatment of these complications and the plan of dosage for the various salts—Ed)

Results of treatment follow Hartfall and Garland who previously reported results in 100 cases, have reported results in 300 83 per cent were "apparently cured" (complete freedom from pain and disability other than that due to bony ankylosis), 69 per cent were markedly improved (some dramatically relieved), 15 per cent slightly improved, 5.6 per cent not improved, 0.3 per cent (one case) made worse, and 1.3 per cent died (four cases) [These deaths include the three noted in their first series, and one additional death from aplastic anemia] Various preparations were used crisalbine, solganol B oleosum, lopion, myocrysin They saw "results which were little short of miraculous in patients showing the severest grades of disability, and a number of those previously bed-ridden became ambulatory, while others discarded their crutches and sticks" Also noted were improved general health and appetite, weight gains, reduction in sedimentation rate Statistics indicated more cures, also more toxic reactions from crisalbine, to avoid which smaller doses than formerly should be used present initial dose 0.05 to 0.1 gm, maximal single dose 0.1 gm, maximal dose for 1 course 1.0 gm

Allochrysine was used by Baker "with uniformly good results" in an unstated number of cases Copeman reported two cases of Still's disease "cured" by allochrysine, which was also given by Crosby to 27 patients with chronic (generally atrophic) arthritis with these results nine greatly improved, eleven improved, three slightly improved, four not improved Crosby concluded (1) that gold therapy is "quite the most potent now available" but (2) it is "attended by not a little risk" and "should only be undertaken when the case is severe enough to warrant such a very real risk which should be explained to the patient before treatment is instituted"

Solganol B oleosum was used by Bach and Slot Bach stated that in early cases "a complete 'cure' may follow with full restoration of function" Half of his (unstated number of) cases "responded well" and the disease became "arrested" after treatment for from three months to two years Of Slot's twelve patients nine improved "satisfactorily," two failed to respond and one patient ceased treatment after a reaction Ellman treated 24 patients with "infective arthritis" with gold (solganol B oleosum) and 14 control subjects with almond oil Both groups noted a beneficial effect but especially those on gold Three of the latter, but none of the controls, were cured The sedimentation rate sometimes rose the first month, then began to sink to normal and remained there, whereas in controls it was variable, dropping only temporarily Tidy noted "undoubted improvement in several cases" but results were difficult to evaluate F. G. Thomson considered it "of doubtful value" (No data were presented)

American rheumatologists have certainly been "off the gold standard", until recently the only comment was that of Cecil (1934) who briefly dismissed his results as "not striking" Holbrook and Hill simply said that their results in an unstated number of cases were "disappointing" Brief reports by Oren and Phillips have appeared Of 66 patients treated by Oren with a water soluble gold salt 60 "responded very well" Results were en-

couraging because of the rapid response to treatment, the slight pain connected with the therapy and the lack of systemic reactions. Five or less courses were given. Phillips treated nine patients with myochrysine, only two were subjectively improved. Because of frequent toxic reactions, initial doses were reduced to 0.01 gm. He concluded that even with small doses the untoward reactions "constitute a hazard which should make us extremely cautious. Personally I do not, for the present at least, feel competent to handle this drug to the advantage of the patient."

(Phillips treated 20 patients: nine with atrophic, eight with hypertrophic arthritis, two with peripheral neuritis, one with subdeltoid bursitis. Of the group only six received a total of 1.50 gm., the amount which many regard as the effective minimum. Tegner, criticizing this report, stated that Phillips' selection of cases was poor — "more than half of his series could, in France and in this country [Great Britain] be regarded as unsuitable for chrysotherapy. One can hardly feel that chrysotherapy has had a fair trial in the United States." Miller's main objection to past reports was the lack of controls in practically all of them. This objection seems valid. Apparently definite benefit results from such therapy in an impressive number of cases, but until more controls are set up we will not know the exact value of the method and how fully justified one is to run the risk of the frequent and rather serious toxic reactions.—Ed.)

Vasodilators Histamine, Choline Subcutaneous injections of histamine acid phosphate were given at first daily, later two to three times weekly for four weeks by Eastwood to 70 patients (27 with atrophic arthritis, eight with osteo-arthritis, five with fibrositis, three with spondylitis, two with gout, 25 "indeterminate and mixed"). Results were analyzed for the whole group: 74 per cent improved, 26 per cent did not. Patients with early atrophic arthritis complicated by vasomotor changes did best. Worst results were in those with no circulatory disturbance. Results were analgesic and psychologic, not curative. Transient relief from pain, stiffness and vasomotor changes were noted. "Although transitory, an immediate response of this type is of value inasmuch as it shows a patient that his condition is not hopeless, that his pain can be removed, that freedom of movement can be restored, so an optimistic state of mind is produced." Shanson noted similar results: "sometimes dramatic and lasting, often transient and disappointing." Side-actions were noted: flushing, headache, sense of warmth, drowsiness, slight fall in blood pressure. Mackenna preferred histamine ionization. Although other types of rheumatism were affected, patients with atrophic arthritis were not relieved, some were made more uncomfortable. The method was discarded for that disease. Mecholyl (acetyl-B-methylcholine chloride, formerly called mecholin) iontophoresis was applied by Mathae to 32 patients with atrophic arthritis, 72 per cent had "good results." It is not a cure but an adjunct. Phillips gave 103 treatments with mecholyl iontophoresis to 20 patients with atrophic arthritis, only two were "improved." It was abandoned as useless. Mecholyl in doses of 50 to 1500 mg. taken orally is an effective peripheral vasodilator, after

its use Goldsmith noted an average maximal rise of 5.8°C in skin temperature of digits. An adequate dose (1000 to 1500 mg) could be repeated every few hours to maintain vasodilation. Histamine was considered useful in early atrophic arthritis by Buckley, of unproved value by Tidy.

Rest and Movement Wide approval of the principles of physiologic and mechanical rest was expressed^{179, 239}. Rest was called "the keynote of therapy,"⁵⁹ "the inevitable price of recovery,"⁵². Many extra hours of bed rest are necessary for the fatigued body as well as the joints of the arthritic.^{223, 431, 529} Inflamed joints should be put at rest in light plaster casts or splints.^{59, 60} Fisher preferred light metal adjustable splints to plaster of paris which has certain disadvantages, it imposes a further handicap on an already poor circulation of the rested part, excludes light and air, prevents easy application of physical therapy and impedes such active, painless motion as the patient may attempt. Kindersley and Burt favored complete immobilization of an inflamed joint for one week in a plaster cast, which is then bivalved and used as a splint. Many will agree with Buckley⁵⁷ "The idea that arthritics should be kept on the move lest their joints 'set' is responsible for much unnecessary suffering and has caused more crippling than it has prevented." Although a prescription for rest is vital when joints are markedly inflamed, as inflammation subsides rest for joints must not be complete lest permanent fixations occur.¹⁸¹ Active and passive painless motion must be encouraged and increased as possible.⁴⁸⁰ Swain described the postural and bed exercises which form the optimal combination with rest. Ghormley reminded us that synovial pannus grows over parts of the joint which are not in contact, if motion can be preserved, prevention of the growth of this pannus may be partially accomplished.

Physical Therapy In the treatment of the various rheumatic diseases, especially atrophic arthritis, physical therapy is widely recognized as "of supreme importance."¹⁶⁴ Thousands of crippled arthritics spend hundreds of thousands of dollars hunting vainly for the "elusive focus" or the medicinal "cure" but spend little or no effort or money on worth-while physical therapy. Other thousands contribute an annual income of \$105,000,000 to the quacks and irregulars licensed by the states to practice the physical methods too many physicians ignore (Hibben). Kling complained that physicians are now apt to over-emphasize the systemic phase of the disease to the extent that they forget to treat the joints as well as the patient, and sometimes even forget to examine the joints. On the tenth anniversary of its origin the Council on Physical Therapy of the American Medical Association noted the present status of physical therapy in this country, outlining principles which should be understood by all physicians concerned with the arthritides. This and other current reports review the therapeutic rationale and physiologic effects of various types of physical therapy for rheumatism.^{117, 173, 322, 324, 448} In Fletcher's opinion physical therapy "deserves the reputation it gained in Europe, not the neglect it has won on this side of the Atlantic."

There is a growing appreciation of the importance of teaching arthritic patients home physiotherapy. Seventy-five per cent of arthritic patients questioned by Hensch²⁴⁸ had previously consulted osteopaths or chiropractors, because their physicians had given them no physiotherapy, or given it haphazardly, "not enough to relieve," or because physical therapy in the physician's or professional physical therapist's office was too expensive, more costly than they could get it elsewhere. The "physical therapy high-brow" may scorn simple home procedures and consider it beneath his dignity to teach his patients the simple adjuvants which would sustain the effects of professional methods. But they are a lot better than nothing and fill the need felt by the patient who has sought relief from a hot bath, a strip of flannel and a hot iron, a farm oven or a bag of heated sand, salt or oats. If his physician does not tell him of better methods he will continue his amateur efforts or get cheap help from cultists. Noting the short sighted attitude of those who insist on "all-professional physical therapy or none" Coulter outlined the simple principles and methods available for the patient's home as well as the physician's office. Others also considered of the greatest importance the formulation and use of suitable methods for inexpensive physical therapy: simple apparatus for heating, methods for passive, assistive and corrective exercises, and for massage^{269, 279, 280, 548}

Many recognized the advantages of *hydrotherapy* and *balneotherapy* but disagreed sharply with the point of view of those spa physicians who seek to create an attitude of superior virtue for the water of a particular spa and who, perhaps to make the patient feel dependent on the spa, make no effort to teach the departing patient home physiotherapy in order to project into the patient's home environment at least some of the benefits of the spa. Miller conceded that spas provide superior opportunities for rest and relaxation and have a psychologic effect "but the water has no more value than that in the home bath tub." In Tidy's opinion "few of the so-called researches from spas have fulfilled the canons of scientific evidence and research." Many spas with widely different waters and climates produce the same results. Unless something more definite, or something common to many spas can be produced with scientific support, the profession and the public may decide the various claims cancel out and that the maximal benefit from therapy can be obtained without visiting a spa. There being no evidence that any ingredients of the water, peat or mud are appreciably absorbed by the skin, results must come from other factors—heat, rest and so forth. Some consider the ordinary hot bath at 100° to 120° F. for 20 to 40 minutes the most useful form of heat⁵⁶⁰. "Electric pads and hot water bottles are a joke, they produce no real benefit." Ellis favored the *Wilde hot bath*. *Ultra-violet* rays as the sole therapy are ineffectual, according to Pringle who favored hot *paraffin wax* baths. *Faradic currents* help to control muscle wasting⁵⁴⁸.

Conventional Diathermy, Short-Wave Diathermy. Ordinary or "long

wave" diathermy utilizes wave lengths from 100 to 400 meters (theoretically from 30 to 500 meters, but no machines currently use wave lengths below 70, few below 100 meters) "Short-wave diathermy" (the Council-approved term synonymous with "short-wave therapy" "short-wave high frequency," "radiotherapy," "radiathermy"), concerns wave lengths from 12 to 30 meters "Ultra short-wave diathermy" (synonymous with "ultra short-wave therapy," and so on) utilizes waves of 3 to 12 meters in length In current dispute are arguments that short-wave and ultra short-wave diathermy are therapeutically superior to ordinary (long-wave) diathermy, that the different wave lengths in the short and ultra short range have different physiologic actions, and that short and ultra short-waves produce effects by a specific effect apart from their heating potentialities Those interested in general and technical details are referred to several papers^{111, 112-114 425, 502} Although some still believe otherwise^{29, 283, 284 315 460} the majority believe results are due solely to the heating effect of short or ultra short-waves, different lengths of which produce identical, not specific, effects^{113, 114 264 337 382} Kovacs concluded that the primary physiologic and therapeutic effects of long and short-wave diathermy are essentially the same, that burns are commonly produced by short-wave diathermy, that short-wave diathermy is technically more convenient but less efficient than conventional diathermy

Ordinary diathermy is useful in arthritis,¹⁵⁰ as useful as short-wave diathermy⁵³⁷ but over-rated⁵⁴⁸ and often disappointing in its effects^{111 112} Beneficial effects from short-wave^{506 582} and ultra short-wave diathermy^{311, 407} were noted in a few cases of atrophic arthritis

(The editors of the reviews believe clinicians in general will share their disappointment at the inadequacies of most "clinical reports" published in certain special journals on physical therapy These reports on arthritis rarely contain data on any controls, they make little or no attempt to differentiate the various types of arthritis being treated, if they do, they contain practically no clinical or laboratory data indicating the extent or severity of the disease from which one can base an independent opinion on the value of therapy As a rule a few representative "successes" are reported in the most cursory detail In technical matters they are often excellent, as clinical investigations they are generally very inadequate and disappointing The variations and vagaries of the arthritides being what they are, it is suggested that specialists in physical therapy team up with clinicians and "rheumatism specialists" to instigate those clinical investigations in physical therapy which are so long overdue—Ed)

Occupational Therapy The importance of occupational therapy as adjuvant to older forms of physical therapy for chronic arthritis needs continued emphasis²⁷⁸ In the management of almost every arthritic patient there is a time or a place when occupational therapy will accomplish results peculiar to itself and more efficiently than conventional physical therapy As Krusen, Macey and Pattee pointed out, these are not mutually exclusive or antagonistic forms of therapy, they should be correlated and interdependent, yet independent Featuring active exercises of a specialized and often highly individualized nature, occupational therapy is a most useful

addition to the more passive types of physical therapy. In the correction of arthritic deformities Cunningham and Shimberg found it very effective.

Roentgen-Ray Therapy Beneficial results from "wide-field roentgen-ray therapy" were noted by Scott in "spondylitis adolescens," but not in atrophic arthritis. Certain cases demand local radiation, others require general radiation. Deep therapy, the use of the more penetrating rays, is needed only for the hip joint, for other joint tissues more superficially situated the less penetrating rays are better. Scott stressed the importance of placing the joint under treatment in the optimal position for exposure of the full joint surface to the rays.

(No statistical results were given—Ed.)

Tidy considered deep roentgen-ray therapy for arthritis of unproved value.

Fever Therapy Effects of fever therapy in atrophic arthritis have been disappointing. Results are better in acute than in chronic atrophic arthritis. Thus, in Hench's survey of reported cases results were as follows: of 21 patients with acute atrophic arthritis, only 10 per cent became symptom free, 40 per cent were relieved. Of 147 chronic cases 10 per cent became symptom free, 25 per cent were benefited. Of 60 additional patients treated by Hench none were cured, only 20 per cent were definitely benefited. Of patients more recently treated, more than 50 per cent received little or no relief. Bierman noted temporary improvement in most cases, permanent results so rarely that fever therapy was not recommended. In the treatment of 40 patients, Stecher noted no cures, in about 30 per cent "substantial results" which were maintained 6 to 12 months. Thus, of 38 cases of chronic, and 10 of acute atrophic arthritis results were "very good" in 16 per cent and 30 per cent, good in 29 per cent and 40 per cent respectively. A fever session in acute cases was five hours at 105° F, in chronic cases three to four hours at 103° to 104° F. Short sessions of low fevers (½ to 1 hour at 101° to 101.5° F) were advocated by Atsatt and Atsatt as "metabolic boosts." (No results were cited.) McClure noted "satisfactory relief" in 46 per cent of 13 chronic cases. Of Neymann's ⁴⁰⁵ patients (not numbered) 15 to 30 per cent were greatly benefited, 30 per cent moderately relieved. Fifty patients were treated by Holbrook and Hill with "disappointing results." None were symptom free, 25 per cent were temporarily relieved.

Climate and Clothing The influence of these factors was discussed briefly by Burt and by Holbrook and Hill. Natives of the Arizona desert rarely develop atrophic arthritis and arthritic visitors have few exacerbations. However, climatotherapy is not a panacea for the disease, all other orthodox measures should be used.

Sympathectomy Bilateral lumbar sympathectomy was performed by McDonald in two cases of long standing Still's disease with marked swelling and deformity of many joints, muscle atrophy and cold, clammy extremities.

Thereafter the patients were more comfortable because of warm, dry legs and feet but "no obvious change was noted in the appearance or in the degree of movement of the affected joints" White recommended the operation only in cases of atrophic arthritis "when it is desirable to improve circulation per se in cold moist extremities" He had noted no relief of pain or increased mobility in five cases so treated A patient of Bothe, affected for six years, bedridden for several months, noted gradual but definite improvement which was notable the first two months after operation and continued thereafter Blocking the appropriate sympathetic nerves by alcohol injections was used by Patterson and Stansby as a substitute for surgical sympathectomy In 11 arthritic patients so treated, satisfactory increases in skin temperature were noted which persisted for an average of six months, average increases being 11.6° F at toes, 10.9° at fingers, 3.3° at knees, 5.6° at elbows Although symptoms of faulty circulation were definitely improved, the results for the joints were "very disappointing" two patients showed definite diminution of the arthritic process, the others showed little or no improvement

In sharp contrast to the above were the results of Young, who performed the operation on seven severely crippled patients with atrophic arthritis with "remarkable improvement" in each Most of them were bedridden, some with "extremely disabling polyarthritis" flexion deformities and "profound disablement of limbs" Noted very shortly after sympathectomy were "rapid relaxation of flexor spasms," banishment of pain, restored power of walking, "practically complete restoration of useful function," "rapid improvement in function of limbs, even of the most disorganized and disabled joints" (the latter comment referring to a case of eight years' duration with "marked deformities—almost complete disablement")

(In view of the past experiences and current reports of others it is very difficult to share Young's enthusiasm Although a brief sentence on the subsequent maintenance of improvement was given in two cases, concerning others in which operation had been performed two to four years ago no subsequent observations were noted Several of the patients noted marked postoperative improvement in upper extremities, nerves to which were not interrupted It was not stated how long this improvement lasted One of us (P S H) has followed all results of sympathectomy for arthritis with particular care as he was associated with Rowntree and Adson from the initiation of this work (1928), indeed helped choose the first and subsequent patients treated by them As a physiologic procedure sympathectomy for atrophic arthritis seemed rational but to those who originated and followed it from its onset it has given clinical results in the main disappointing Adson's current comment follows—Ed)

According to Adson "cervicothoracic and lumbar sympathectomy have been of value only in relieving symptoms and checking the disease in a small group presenting definite disturbances of sympathetic origin, characterized by vasoconstriction and hyperhidrosis The operative treatment does not alter deformities, contractures or the condition of ankylosed joints It

is of no value in the treatment of arthritic processes in larger joints—knees, elbows, hips and shoulders "

Bone Puncture (Forage) Further favorable results from bone puncture were reported by Mackenzie His reason for adopting this procedure (1931) was given previously²⁴⁵ an elderly arthritic patient, long crippled, broke a femoral neck, during convalescence her arthritis became, and remained, painless Mackenzie's procedure was an empiric approximation of this phenomenon He concluded that atrophic and hypertrophic arthritis ("essentially the same in origin") are the results of primary osteitis, arthritis being secondary thereto Treatment consisted of drilling "sufficiently large" holes in para-articular bone—in the lower end of the femur and upper end of the tibia when knees were involved, in the femoral neck, trochanter and acetabular margins when hips were affected Some marrow is scooped out "the whole idea being to bring about a state of decompression" In a typical case of "osteoarthritis" clear, oily fluid, "definitely under pressure," wells up, in it are white granules often larger than the head of a pin Cultures and microscopic examination of this material revealed "nothing of interest" After operation convalescence was generally uneventful The operation was done for hips or knees of 106 patients, statistical results were not given but "an improvement really worth while can be expected in 80 per cent of cases" The cause of relief was not known

(This procedure is not new in 1890 Noble Smith reported good results from "bone drilling in the neighborhood of inflamed joints and elsewhere" Similar results have been reported recently from France by Graber-Duvernay, 1932, 1933, 1935 definite improvement in seven of ten cases Simpson and Henderson noted "lasting relief from pain" in three of twelve cases of "hypertrophic osteo-arthritis" of hips, lesser improvement in four others—Ed)

Prevention and Correction of Deformities The well-known procedures for the correction or prevention of deformities were again reviewed^{59, 239 200, 288, 306, 368, 384, 480, 529, 530} They included the use of plaster splints and braces, and various operative procedures Discussed were the best type and safe duration of immobilization³⁰⁶ the use of oxygen insufflation to prevent or correct adhesions,^{257, 209} optimal positions for ankylosing joints, also for those where retention of function is anticipated^{239, 480} Points which cannot be too often emphasized were that with the cooperation of the physician and orthopedist deformities generally can be prevented by early treatment, or can be largely corrected once they have occurred, and that functional use of deformed joints can be restored by suitable orthopedic surgical and non-surgical procedures^{179, 250, 529, 530} Too often so-called cooperation between physician and orthopedist is merely a matter of lip-service, to be successful it should be vital, continued from the onset of the disease (Fisher) The various causes and types of adhesions were ably discussed by Jones adhesions may result from too little or too much motion of joints, from uncorrected edema, from joint manipulation or over strenuous physiotherapy

Besides the placing of pillows under knees, the "shortest route to the wheel-chair" is accomplished by the patient with painful bent knees who keeps walking no matter how much it hurts (Holbrook and Hill). When cartilaginous destruction has occurred, manipulation (active, passive or surgical) must be done with caution. Henderson stated, "If a joint is more or less fixed at a certain angle and use only changes that angle to another fixed angle, one must not manipulate it. When the range of motion is increasing one should trust to active motion, when it is not increasing, then only should passive movements be carried out, but not forcible manipulation." Manipulation under anesthesia requires more experience than any other procedure, one of the last things a young orthopedist should be encouraged to do. In an instructive paper Lewin listed 18 do's and don't's in manipulation of arthritic joints. For the correction of flexed knees some believed posterior capsulotomy often necessary in addition to the use of manipulation and bivalved splints.^{57 269} Of 19 cases in which such treatment was given results were successful in 14 (Holbrook and Hill).

Psychotherapy Little attention has been paid to this factor, which is such an important and (from the standpoint of evaluating clinical results) so often an unrecognized feature of any treatment scheme. It is imperative that the patient be taken into his physician's full confidence and vice versa, that the patient be instructed fully in the problems that lie ahead, that he know the limitations and possibilities of his own and his physician's therapy, that the reason for good results but particularly for the bad results (which patients see about them and inevitably remember) be frankly discussed (Fletcher, Ellman). Social, emotional and economic adjustments are often required that the patient may be properly conditioned for the prolonged treatment so often necessary for success. Both physician and patient must realize there is no easy way to a "cure." Physicians should stop treating patients half-heartedly with each new remedy of doubtful value and concentrate on the few simple measures of proved worth.²⁶⁹

Prognosis, End Results According to Pemberton, 75 per cent of arthritic patients should experience great betterment or complete arrest, 20 per cent are more refractory perhaps because of a dominant continued infection, in 5 per cent therapy is of no avail. In Sweden a plan of hospital treatment and subsequent occupational adjustment has been set up. According to Kahlmeter, 70 to 80 per cent of patients leave the hospital fit for work. Enduring results were relatively frequent. 62 per cent of 1000 patients were earning all or part of their living three or more years after hospitalization. Other figures noted by Kahlmeter were those of Zimmer (57 per cent "definitely improved"), of a Silesian Insurance Institute (80 per cent relieved), of Danischewsky (52 per cent working) of Freund (36 per cent cured, 45 per cent improved). Of 452 generally "completely helpless" patients with atrophic arthritis discharged from the Robert Brigham Hospital, Boston, about 66 per cent of those living in 1935 were working,

21 per cent had had relapses (Kuhns and Joplin) The commonest diseases complicating convalescent care were arteriosclerosis in 41 cases, nephritis in 22, hypertension in 19, obesity in 17, myocarditis in 16, gonorrhea in 12, rheumatic heart disease in 10 There were 76 deaths, 18 from pneumonia, 13 from myocarditis, 11 from nephritis, 6 "postoperative," and 28 miscellaneous

HYPERTROPHIC ARTHRITIS

Definition In the following discussion "hypertrophic arthritis" means a clinical syndrome, not just a roentgenographic alteration, it is synonymous with senescent degenerative osteo-arthritis, or "primary osteo-arthritis" ⁵⁹, ²²⁵ as contrasted to secondary (hypertrophic) osteo-arthritis which may appear as the (radiologic) end result of many articular disorders, among them gout, late atrophic arthritis or gonorrheal arthritis in weight bearing joints

(The merits and demerits of the various terms for this disease were critically reviewed by Bauer and Bennett The term "hypertrophic" is not satisfactory because the hypertrophic changes are a relatively late feature of the disease, much later than its degenerative feature, nor is "hypertrophic" distinctive because many types of arthritis may show hypertrophic changes, for example, gout, hemophilia, Charcot joints, and so forth ¹⁷⁸ "Senescent" is a better term and is usually, but not always, appropriate, as the disease may, under unusual circumstances, appear long before senescence The word "degenerative" describes the primary phenomenon of the disease, is therefore peculiarly fitting and should be retained in the final designation "Arthritis deformans" is not distinctive since other forms (for example, atrophic) may be even more deforming The term "arthritis" has been objected to since there is little or no evidence of inflammation, hence, some have suggested "arthrosis" or "osteo-arthrosis" which literally translated means "a joint full of bone" For various reasons therefore the term "degenerative joint disease" seemed preferable to Bauer and Bennett, until a term based on the ultimate etiology of the degeneration is known—Ed)

Incidence The studies of Bauer and Bennett, and others revealed that with each succeeding decade in life beyond the second, certain joints, especially knees and joints of the spine, show "degenerative arthritis" with increasing frequency so that the disease is pathologically universal after the age of 40 to 50 although it may be clinically apparent (that is, symptomatic) in only about 5 per cent

Clinical Features, Symptoms Of Haden and Warren's 50 consecutive cases the age incidence was from 34 to 69 (av 51) years in females, 34 to 58 (av 52) years in males Females were affected symptomatically five times as often as males (42 females, 8 males) In the cases which Bauer and Bennett studied at necropsy the patients had presumably never had significant symptoms although joints were often markedly affected It is common to find marked hypertrophic changes in one joint which is practically painless, and to find only slight radiologic changes in another joint which is very painful Why is one painful, the other not? Some believe the pain is due to superimposed infection According to Bauer and Bennett two

factors are responsible for pain. When marginal tissue is proliferating the periosteum may become elevated and cause pain. Once the marginal osteoid tissue ceases to proliferate and becomes calcified pain may also cease. The second factor in pain production is related to altered mechanics, occasional loose bodies, or the pinching of sensitive synovial villi. Gordon, however, blamed two other factors for the pain: (1) exposure of soft subchondral bone by cartilage destruction, and (2) presence of muscle spasm from the fibrositis which almost invariably accompanies hypertrophic arthritis. Buckley reminded us that patients with affected hips often have no pain therein, pain being referred to the knees which, in spite of normal motion and roentgenograms, are sometimes long treated for arthritis nonexistent therein.

Roentgenograms. The characteristic and differentiating radiographic features have been discussed. Spurs and exostoses, commonly present at muscle insertions, are but the "perfectly natural strengthening of ligaments at their insertions" and should not be misinterpreted as "osteo-arthritis"—a mistake often made even by radiologists, according to Gordon, to whom the essential roentgenographic feature of hypertrophic arthritis is the presence of osteoporotic areas in or about articular bone.

Pathology. The well-known pathologic features were reviewed by several^{194, 196, 200, 200}. In particular, Bauer and Bennett reviewed their development in the human and animal (spontaneous and experimental) forms of the disease.

Laboratory Data. Anemia is rare, only 4 per cent of Haden and Warren's 50 patients had hemoglobin below 75 per cent (11.5 gm per 100 cc). The neutrophile nuclear count usually does not show a left shift in hypertrophic arthritis as it does in atrophic arthritis. But such a shift was noted by Collins in 30 per cent of 11 cases of hypertrophic arthritis of hips and seemed to bear a definite relationship to bone cysts in hip joints. Accepting Ely's view that the cysts were areas of aseptic necrosis, Collins suggested that toxic absorption of some kind must proceed from these cysts, for when they were large, that is, with a large surface from which absorption might take place, the nuclear count showed a marked left shift, when cysts were small or scarcely apparent, the nuclear count was normal. Hartung and co-workers noted that the nonfilament count, which was always elevated in atrophic arthritis, was normal in 53 per cent, elevated in 47 per cent of cases of hypertrophic arthritis "perhaps due to associated rheumatoid disease or focal infection."

In contrast to atrophic arthritis the blood proteins are essentially normal in hypertrophic arthritis (Davis). The sedimentation rate was slightly elevated in 7 of Davis' 11 cases, normal in 80 per cent of Haden and Warren's 50 cases. Fasting blood sugar levels were usually normal, 22 per cent of the 50 patients had diminished sugar tolerance.

The cytology of synovial fluid in hypertrophic arthritis is strikingly dif-

ferent from that in atrophic arthritis Collins noted a low absolute polymorphonuclear count in each of three cases, implying an absence of synovial inflammation Total nucleated cells per cu mm were 210, 900, 5800, polymorphonuclears 4.5 to 14 per cent

Contrary to the opinion that effusion is rare, Kling found in "osteoarthritis" periodic marked increases of synovial fluid with a high viscosity and a small number of cells, chiefly monocytes and synovial lining cells, indicative of synovial hypertrophy and hypersecretion

Etiology and Pathogenesis No new views on etiology were expressed The disease is presumably a degenerative process resulting not from one specific factor but from the wear and tear of increasing age, in other words, it is caused by life and the process of living^{28, 59, 83, 181, 225} It is fostered by certain predisposing factors, hastened or made symptomatically active by other factors Current writers differed only in the individual importance they ascribed to the different precipitating factor of heredity and constitution (that is, inheritance of vulnerable cartilage) or of the following accelerating factors abnormal metabolism, circulatory deficiency to joints, various traumas, toxemia from infection, nutritional deficiency of articular tissues, gastrointestinal disturbances, exhaustion, alcoholism^{181, 225} Some regarded the factor of trauma as the most important, and assigned no rôle to infection, metabolic disturbances or endocrine dysfunction (Bauer and Bennett) Others (Haden and Warren, Fletcher) stressed the importance of metabolic or nutritional factors

Heredity and Constitution Anthropometric studies by Kovacs and Hartung indicated that patients with hypertrophic arthritis tend to have increased horizontal measurements, short thick necks, massive silhouettes, chest circumferences greater than abdominal Ellman and Mitchell found slight, Kovacs and Hartung found no, psychologic differences between patients with atrophic and hypertrophic arthritis

Patients may inherit the tendency to hypertrophic arthritis by inheriting tissues susceptible to degeneration (O'Brien) In cases in which hypertrophic arthritis comes on prematurely it is possible that premature senescence of cartilage has set in, cartilage aging faster than the rest of the patient's tissues Thus Bauer and Bennett suggested that the type of cartilage one inherits governs in part the age of onset of hypertrophic arthritis and the rapidity with which it develops If one inherits "good cartilage," hypertrophic arthritis may be long delayed in spite of the operation of the usual predisposing and aggravating factors Considering the hereditary factor most important, Haden and Warren were unable to evaluate it in their patients because family histories of "arthritis" were so unreliable

Trauma Several^{28, 208} regarded the dominant factor to be a variety of "microtrauma," that from obesity, overuse through occupation or recreation, malposture, congenital deformities or other mechanical defects Gor-

don saw a close relationship between juvenile disorders—congenital hip disease, coxa plana, slipped epiphysis, Perthe's disease—and hypertrophic arthritis of hips late in life Of Haden and Warren's 50 patients with hypertrophic arthritis 62 per cent were an average of 25 pounds overweight, a source of physical strain to weight bearing joints Bauer and Bennett particularly stressed the factor of trauma Hypertrophic arthritis was readily produced by altering the apposition and weight bearing of joints in animals Certain patients were found to have marked hypertrophic arthritis in one joint subject to unilateral occupational or postural trauma, but none or very little in the opposite joint Thus hypertrophic arthritis may result in one knee more than its fellow, from loose bodies, knock knees, bow legs, intra-articular fracture, a pronated foot

Impaired Circulation Many assumed that hypertrophic arthritis may be due to deficient articular circulation, the circulation being impaired because of hypotension or, more often, of hypertension and arteriosclerosis Buckley⁵⁸ noted the frequency of osteo-arthritis of hips in horseback riders due possibly not to trauma but to obstruction of the blood supply through compression of the artery of the ligamentum teres owing to extreme abduction of the hip According to Gordon the disease occurs in those whose vascular system is beginning to deteriorate, not necessarily generally, but locally, in the region of one joint or one limb "This vascular deterioration leads to a relative malnutrition and consequent degeneration of structures whose blood supply is defective, and this is the primary cause of osteoarthritis"

(No data proving these ideas were given—Ed)

Of Haden and Warren's cases none of the 8 males and only 24 per cent of the 42 females had a systolic blood pressure more than 140 to 145 mm of mercury Nevertheless they concluded "the frequent observation of calcareous deposits in arteries, the common finding of arterial hypertension, and the well-known gradual decrease in capillary bed with age, all emphasize the circulatory factor"

Monroe and Walcott compared 257 patients with hypertrophic arthritis to "normals" of similar age and noted the following respectively cardiac enlargement in 18 per cent of arthritic patients, in 4 per cent of controls, hypertension respectively in 39 per cent and 8 per cent, arteriosclerosis in 16 per cent and 18 per cent, varicose veins in 15 per cent and 8 per cent They concluded that cardiovascular disease occurs with increased frequency in patients with hypertrophic arthritis

(The conclusion does not seem justified Arteriosclerosis was not present in an unusual number of cases—Ed)

Bauer and Bennett admitted that vascular deficiency might be a factor but in the study of knee joints of persons with hypertrophic arthritis who died at various ages arteriosclerosis was not found to be an important feature

Endocrine Disturbances Some⁴¹⁵ vaguely incriminated "an endocrine

imbalance of thyroid and ovaries," but, as Bauer and Bennett stated, no proof exists that endocrine disturbances alone ever produce the disease. Of Peer's 28 cases the metabolic rate was below — 9 in 60 per cent, below — 14 in 3 per cent (below — 19 in 2 cases)

(No normal controls of similar age were studied. His results in the atrophic group were essentially similar—Ed.)

Of Haden and Warren's cases metabolic rates were (slightly) above normal in 16 per cent, below normal for their age in 84 per cent, the average decrease below normal was 15 per cent.

(Most patients were given only a single determination. The analysis as given was not complete enough for conclusions—Ed.)

Miller believed that endocrine disturbances may cause the obesity but not the arthritis, except indirectly.

Metabolic Disturbance Peers found no disturbances of sugar metabolism of etiologic significance. Indoluria was noted by Forbes and associates in 10 of 13 cases of hypertrophic arthritis as well as of atrophic arthritis. Because of this and because five of eight patients treated with a high sulfur, low carbohydrate diet "improved," a disturbance in hepatic function and in sulfur metabolism was suspected. Six patients studied by Rinehart, Greenberg and Baker showed no evidence of vitamin C deficiency, indeed their plasma ascorbic acid content was high 0.90 to 1.34 mg per 100 c.c.

Factor of Infection Patients with hypertrophic arthritis present little direct or indirect evidence of infection. Practically none of the patients of Haden and Warren had been seriously ill within five years of the onset of arthritis. Only 42 per cent had *foci of infection*, a small per cent for the age of the group. *Blood cultures* from 39 patients of McEwen, Alexander and Bunim were positive (all for green-producing streptococci) in 26 per cent, a finding considered incidental. Patients with hypertrophic arthritis do not often possess *agglutinins* either to hemolytic or green-producing streptococci in significant titer. McEwen, Alexander and Bunim found agglutinins to hemolytic streptococci in none of 46 patients. Hartung and associates noted agglutinins to green-producing or hemolytic streptococci practically never (in a few cases to one green-producing strain only). Agglutinins to hemolytic streptococci were found by Goldie and Griffiths in a dilution of 1:100 in only 10 per cent, 1:200 in 5 per cent, 1:400 or more in none, to green-producing streptococci in dilutions of 1:100 in 5 per cent, in higher dilutions never. *Precipitins* to hemolytic streptococci were present in serum of 10 per cent of 21 patients²⁴³. They were present in 18 of the 30 cases of McEwen and associates (reaction slight in seven, definite in seven, marked in four, very strong in none).

Antistreptolysins More than 100 units were not present, according to McEwen and associates (46 cases), Dawson and Olmstead (24 cases), Goldie and Griffiths (30 cases). *Antifibrinolysins* were absent in all of

Stuart-Harris' six cases, in 62 per cent of 13 cases of McEwen and associates (they were weakly present in 38 per cent) *Skin tests* with hemolytic streptococci were negative in 100 per cent, those with green-producing streptococci were negative in 97 per cent of the 30 cases of Goldie and Griffiths

In spite of this mass of negative evidence others believed that infection might play some rôle Poynton⁴³⁹ stated that osteo-arthritic changes may be produced in animals by injecting streptococci intravenously Irons had seen Heberden's nodes become acutely tender, red and swollen following a respiratory or other infection According to Holman the absence of a pathologic reaction of inflammation does not entirely rule out the rôle of infection

Treatment Since cartilage has little or no capacity for repair, little can be done to replace significant cartilaginous destruction or to "cure" the disease But much can be done to lessen pain, perhaps to stop or slow the progress of the disease by correcting accelerating and causative factors^{28, 58, 225} Measures should be (1) to relieve strain and trauma of all sorts, (2) to check factors which favor degeneration Given a chance, nature will repair many of the cartilage defects after a fashion (with fibrosis), the repair at best is a poor substitute for the original cartilage but often the joint will be as useful as ever (Ghormley) Some will be limited, a few will become markedly limited True ankylosis does not occur but "artificial ankylosis" may result from interlocking osteophytes Reassurance is one of the most important features of treatment, patients must be told they are not headed for crippledom and a life of invalidism

Many of the measures indicated in atrophic arthritis, particularly the more strenuous ones, are not suitable in hypertrophic arthritis According to Bauer and Bennett, there being "no evidence favoring infectious, metabolic or endocrine theories, these patients should not be subjected to wholesale removal of foci, administration of endless sera and vaccines, endocrine therapy, colonic irrigations, hyperpyrexia, weird dietary regimens, etc" However, Pemberton believes that measures effective in atrophic arthritis are equally applicable in hypertrophic arthritis

Reduction of trauma of whatever type is indicated Bed rest is often very useful, but rest should not be complete, joints should be moved through their full range of motion frequently^{28, 58, 431} Bandages or caliper splints may provide special rest for hips or knees, and corsets or braces for the back⁵⁸ However, "it is often difficult to persuade the conservatively minded and short-tempered old lady or gentleman to harness themselves with 'this piece of damned iron-mongery'" (Gordon)

Obesity being a common source of trauma, weight-reduction diets were generally advised^{28, 58, 225} Two patients, given a raw vegetable diet, noted some relief at first, relapses later²³⁷

Massive doses of vitamin D alone were given by Livingston to three patients, in conjunction with fever therapy to four other patients, two of the former and all of the latter were "improved"

Some saw no indication for removal of foci,²⁸ others removed them conservatively for general reasons. Gordon wrote, "If the physician can persuade himself that a focus of infection is contributing to the general degenerative process, then such a focus should be removed so long as the strain involved in its removal does not prove too much for the frequently elderly and sometimes feeble person, so that he dies of his cure." Kovacs gave various vaccines in 42 cases; improvement was noted in only a few, some patients were made worse. Foreign-protein therapy seemed useless.²⁰⁸ Cases of hypertrophic arthritis were considered suitable for bee-venom therapy by Mackenna [no statistics given].

Iodine was prescribed by Buckley, given orally or intramuscularly as lipiodol "to provide a reservoir of the drug from which absorption into the circulation continually goes on with definite relief of pain and stiffness in many instances." Intramuscular injections of sulfur gave "considerable recovery" to only two of Krestin's five patients. Sulfur, given in a high sulfur diet, "markedly improved" five of eight patients of Forbes and associates.

Gold therapy is "useless," "unsuitable" in hypertrophic arthritis^{14, 18, 538}. Only two of eight patients of Phillips noted subjective improvement. However, Slot noted "beneficial results" in some cases, and 13 of Oren's 22 patients "responded well." Gordon regarded "the precious metal more obviously beneficial to the physician than to the osteo-arthritic patient." Histamine injections were recommended by Eastwood and Shanson, histamine ionization by Mackenna, 9 of whose 13 patients noted reduction of pain and stiffness.

Roentgen-ray therapy was considered useful^{164, 183, 477}, it is presumably analgesic, reduces congestion, and causes absorption of pathologic fibrous tissue.

(Very few, if any, controls were used in the evaluation of most of these forms of treatment, details given were very meager—Ed.)

Fever Therapy Of 64 patients treated by Davison, Lowance and Barnett, 44 were "markedly relieved," 13 "definitely relieved" and 7 not relieved. To the "great surprise" of Warren and Lehmann "several cases" of hypertrophic arthritis were "markedly relieved over a long period of time" after a single artificial fever at 40.5° C for 4 hours. Others considered cases of hypertrophic arthritis unsuited for fever therapy. The patients do not react well, and during such therapy may develop "delirium and other terrifying states."^{405, 406} According to Hench's summary of reported results in 74 cases, only 5 per cent of patients became symptom-free.^{249, 250}

Physical Therapy The usual varieties were recommended. Several favored hydrotherapy,^{58, 104, 183, 208} especially the use of warm pools, it relieves the muscle pains and spasm of associated fibrositis. Relative merits of different forms were described.^{58, 148} Patients with hypertrophic arthritis are particularly in need of simple methods for home physiotherapy which

Coulter described Short-wave therapy gave temporary relief in a few cases ^{506, 582}

Sympathectomy This is not indicated in senescent hypertrophic arthritis according to Adson. However, Young noted "rapid amelioration of pain" and "substantial improvement" in motion of the hip of a 62 year old woman who was so painfully crippled that she requested the procedure.

(Because of temperature gradients existing in legs, skin temperatures about hips and thighs are altered but slightly after sympathectomy. It is unlikely that in Young's case relief was due to sympathectomy per se, it was probable that from any operation, the effect of anesthesia, bed rest, convalescence—Ed.)

Bone Puncture "Osteoarthritis and rheumatoid arthritis belong to the same type of disease" according to Mackenzie, who obtained "worth while improvement" by bone puncture in 80 per cent of 106 cases (types not separately analyzed). This was discussed under the treatment of atrophic arthritis. Simpson and Henderson noted "definite benefit" in seven of twelve cases of osteo-arthritis of hips (for more than six months at time of follow-up) in which bone drilling of the neck of the femur was done, only one of ten patients subjected to trephining by Ducker noted improvement. Contrary to Mackenzie's experience, Ducker noted exacerbation, not relief, of symptoms of osteo-arthritic hips after spontaneous fracture of femurs.

Orthopedic Procedures Indications for cheilotomy, osteotomy, arthrodesis, arthrotomy, acetabuloplasty, and plastic procedures on the head of the femur were given ^{178, 255}. In selected painful cases of monarticular hypertrophic arthritis of hips, Malkin noted good results from femoral osteotomy. Arthrodesis seemed most satisfactory to Gordon.

For the relief of pain in hips Slot recommended epidural injections of 1 per cent procaine.

BACKACHE

There have been two schools of thought as to the cause of backache. "The cause of most backaches is anywhere but in the back." According to this, the older school, pains in the back most often arise from distant infection or from gynecologic or urologic diseases. According to the newer or "mechanistic school," the cause of most backache is in the back (Milliken). Backaches are described as of medical, orthopedic, urologic, neurologic or gynecologic origin. Data on the commonest causes of backache are difficult to obtain. Published statistics must be interpreted in the light of the writer's specialty. The internist, orthopedist and gynecologist will differ on "the commonest cause." Kuhns considered trauma, faulty posture and fatigue the most frequent causes. According to Albee myofascitis is the commonest cause, Hartung considered most backaches due, not to one factor, but to a combination of postural, arthritic, traumatic and congenital factors.

Postural Backache Milliken believed that one may "assume the case to be postural if no other pathology is found" on careful examination. According to Brown, in the drooped position of the thorax seen in faulty body mechanics it is possible to get pressure or stretching of the intercostal nerves with radiating pain. This pressure may come from acute or chronic inflammation due to strain of the costovertebral or costotransverse joints. According to Henry, poor abdominal musculature permits increased sacral inclination which, whether it is the cause or result of faulty body mechanics, throws a strain on the lumbosacral ligaments and articulation. According to Hartung, exaggerated lumbar lordosis is the cause of most postural defects. Indiscriminate exercise is valueless, exercises recommended are those which tilt the front of the pelvis up and the back of the pelvis down.

Sacro-Iliac and Lumbosacral Strain Sacro-iliac strain and dislocation as causes of backache have been greatly exaggerated^{241, 307, 370}. The pathogenesis, symptomatology and treatment of lumbosacral strain and its differentiation from sacro-iliac strain were reviewed^{374, 375}. "Sacrarthrogenetic telalgia" was the formidable term applied by Pitkin and Pheasant to "the typical syndrome of pain which originates in the sacro-iliac and sacrolumbar articulations and their accessory ligaments". Under this heading were given a study of referred pain, sacral mobility, alternating scoliosis, differential diagnosis of "sacrarthrogenetic scoliosis" and treatments used in 1000 cases of low back pain.

"Post-Operative Backache" This is most often caused by the inadequate support of lumbosacral muscles in a sagging bed. Berman prevented it "easily" by incorporating a new "movable semicircular spring unit" in regular hospital beds.

Uterine Displacements These often cause backache, according to Dicks. "Backaches above the lower lumbar and sacral regions have no direct relationship with pelvic disease". However, Holt believed pelvic disease was a rare cause of backache. "The backache most frequently associated with kidney conditions is felt in the costo-vertebral angle particularly over the superior lumbar triangle"⁴⁴⁰.

Myofascitis An infectious or toxic inflammation of muscles and tendons of the lower back is one of the commonest causes of low backache according to Albee. Kuhns considered it a rare cause of low back pain. Lumbago represents acute or chronic myofascitis^{150, 151, 241}.

Other causes of low back pain and secondary sciatica were discussed: the rôle of congenital anomalies such as spondylolisthesis, lumbosacral transitional vertebrae, posterior displacement of the fifth lumbar vertebrae, and so on^{27, 206, 241, 305, 375}; coccygodynia³⁰⁵; contracted iliotibial bands and fasciae producing low back pain and sciatica^{413, 414}; diseases of intervertebral disks and conditions secondary thereto^{16, 146, 227, 256, 352, 373, 404}.

Clinical and radiologic features of *neoplastic diseases* of the spine were given^{186, 216, 365, 459}. Fray discussed radiologic differences between infection

and malignancy in cases in which there is a dorsal paravertebral mass. Important radiologic features of malignancy were preservation of articular plates in the presence of collapse of the body, slight or no narrowing of disk spaces in cases of marked collapse, absence of wedging resulting in little or no kyphos, diffuse increase in bone density, and involvement of vertebral appendages. Normal roentgenograms may be obtained in the presence of metastatic foci of malignancy, for the latter are visible in roentgenograms only when large enough to produce a definite contrasting shadow or when marked osteosclerosis occurs about the metastasis.²¹⁰ Cases of vertebral involvement in Hodgkin's disease were reported.⁴⁵⁹

Diseases of Intervertebral Disks The muscular, ligamentous, neural and osseous components of the spine are so closely related anatomically and physiologically that no one part lives unto itself alone. In last year's Review we gave a detailed presentation of the "newer anatomy of the spine," the physiology and pathology of intervertebral disks and posterior facets, and diseases secondary thereto. Current reports contain little different, several^{227, 289, 461} reviewed the subject. Certain changes in intervertebral disks may be quite unrelated to a patient's complaint and a given backache must not be incautiously ascribed to such changes found in roentgenograms. Many variations in disks do occur but the consensus of opinion seems to be that many disk changes are of little significance.²⁵⁶ According to Bailey and Taylor herniation of the nucleus pulposus or the disk usually occurs into a vertebral body, rarely results from sudden trauma, is usually a degenerative process from wear and tear, and is seldom of clinical significance. Herniation of a disk in any other direction than into vertebral spongiosum is often related to sudden trauma and may cause pressure on the spinal cord.

Recently narrowed or ruptured disks have been considered the cause of a wide variety of complaints—compression phenomena, sciatica without neurologic changes, and pains and aches of varying severity about the lower back. Sashin's patients with narrowed disks complained mainly of dull aching pains in the lower back, often of sciatica. They usually gave a history of mild injury, a slight fall or sudden twist. They walked guardedly with stiff, often tilted spines, and had lumbosacral and gluteal tenderness. Lateral and oblique radiographic views of the spine revealed the narrowed disk. Sashin's treatment aimed to reestablish normal lumbar lordosis and to support the spine by rest in a plaster bed or jacket. No manipulation was used.

(Four illustrative cases were given. Narrowed disks were present but the evidence seems insufficient for us to conclude that symptoms in these four cases were actually due to the narrowed disks. Detailed results of treatment were not given.—Ed.)

Narrowing of a disk does not necessarily indicate a protruded disk, narrowing may occur from degeneration and fibrosis of the disk without protrusion, and posterior protrusion may occur without narrowing. In-

deed, according to Camp, narrowing of the intervertebral space at the site of a protruded disk occurs in only a small percentage of cases. Therefore ordinary roentgenograms are only suggestive and of limited value in the diagnosis of herniated disk. In Love's series of cases in which operation was performed, protrusion occurred in any region of the spine, especially the lumbar region. Commonest symptom was sciatic pain. The diagnosis was easy in the presence of neurologic findings: motor weakness, sensory loss, signs of a compression-level in the cord. The diagnosis is difficult in the presence of pain only, with no neurologic findings, it then depends on fluoroscopic and roentgenographic examinations of the spinal canal after subarachnoid injections of lipiodol. One should not do this to all patients with obscure back pain. Love advised it only for the following patients: (1) those whose pain follows the distribution of one or more spinal nerve roots for a considerable period of time and who have not been notably relieved by orthodox conservative treatment, (2) those whose cerebrospinal fluid contains more than 40 mg total protein per 100 c.c. fluid and reacts positively to a test for globulin (Love admitted, however, that protruded disks with compression phenomena do occur in patients with normal or even low values for total protein in spinal fluid), and (3) those who demonstrate a "reversed Queckenstedt test." This is the most important of all criteria for the use of lipiodol intraspinally, and at times, according to Love, gives the only real clue to the cause of the trouble. [The technic and interpretation of the test were given.] The absence of an increase in the manometric reading and an unbearable pain response provides a pathognomonic sign of a mass pressing on caudal roots. If the protruded disk corresponded to the level of the root pain complained of, then and only then was surgical treatment (laminectomy) performed, for disks can herniate without causing pain.

Intervertebral disks may be injured by lumbar puncture, with subsequent production of symptoms (Pease, 1935). Milward and Grout noted five patients operated on under spinal anesthesia, who at varying intervals (immediately, three weeks, five weeks, four months, six months) after operation, complained of severe pain in the back, occasionally in the lower limbs. They could not stand or sit fully erect. Spasm of lumbar muscles and marked tenderness over one or more lumbar vertebrae were present, in one case, with transient urinary retention. Roentgenograms (well illustrated) showed a rapidly progressive lesion, a progressive arthritis localized to one intervertebral joint, loss of joint space, new bone formation between edges of adjacent vertebrae. Milward and Grout favored Pease's explanation: the needle puncture traumatized the annulus fibrosus with rapid (in children) or slow (in adults) escape of the nucleus pulposus and the subsequent development of localized arthritis.

An unusual case of herniation of the intervertebral disk between the sixth and seventh cervical vertebrae complicated by a localized staphylococcal in-

tection and fatal compression of the cord was reported by Dickson. Hadley again described the possible results of degeneration of disks: thinning of disk, closer approximation of vertebral bodies producing (1) a localized kyphosis if posterior articulations do not slip past one another, (2) apophyseal subluxation with reduction in the size of the intervertebral foramina and production of radiculitis, or (3) actual bony impingement between the tip of the articular process and the pedicle above, or the lamina, below (all illustrated in the report). Hadley described a new point in the radiologic diagnosis of apophyseal subluxation: distortion of an "S-line."

General Measures for Low Back Pain Measures discussed were the institution of rest, relaxation and support for the spine, the use of proper beds, strapping, heat, massage, belts, corsets, braces (not to be worn too long), proper shoes, exercises to improve body posture and to strengthen abdominal and spinal muscles^{256, 303, 320}. Correct treatment presupposes a correct diagnosis, which is not an easy matter, and can be made only after a thorough physical and radiologic examination. Lewin in particular described with diagrams and photographs the various physical signs and tests useful in differentiation of lumbosacral, sacro-iliac and adjacent diseases. In special cases manipulation for low back pain is most useful^{241, 305, 341}. The indications, contraindications, technic and after-care of manipulation were given in detail by Lewin.

Epidural injections of procaine seemed of little value to Kimberley. Special indications for facetectomy, fasciotomy, and lumbosacral fusion were given^{206, 338, 370}.

SCIATICA

Classifications of sciatica were reviewed³⁶. Douthwaite used a familiar one: (1) sciatic neuritis, acute or chronic—(with neurologic changes), (2) central sciatica, acute or chronic (as a rule without neurologic changes) often called by others "secondary sciatica" or "sciatic pain". The latter is generally secondary to disturbances in the lumbosacral region. "Real sciatic neuritis" with neurologic changes in sensation and reflexes, and muscle atrophy in thigh or calf are rare, according to Henry, who regarded the commonest form of sciatica to be usually a symptom, not of nerve trunk disease but of hamstring spasm or irritation of the piriformis muscle from arthritis or other cause. Douthwaite wrote of the possibly serious significance of bilateral sciatica: "Any patient with sciatic pain in both legs must be suspected of a central—e.g. vertebral, spinal or pelvic disease, not forgetting the very real possibility of a cauda equina tumor." All other examinations including that of cerebrospinal fluid must be negative before accepting a diagnosis of "simple" bilateral sciatica.

Causalgia (neuralgia characterized by intense, local, burning pain) rarely affects other than the median nerve, the tibial portion of the sciatica, and less often the ulnar nerve. Karnosh reported two cases which supported the view that sciatic causalgia results from ischemia of the nerve trunk.

Ten days after striking his right gluteal region and developing a hematoma, a patient began to complain of paroxysmal burning, dragging pain in a heel, extending into the calf. At exploration it was found that the nutrient artery to the sciatic nerve had been severed. Another patient developed sudden burning paresthesia of a foot while at work. For reasons given a diagnosis of sciatic causalgia from thrombosis of a nutrient artery was made.

Treatment The usual measures of heat and rest were advocated. For "rheumatic sciatica," polyvalent streptococcal vaccine suspended in oil (lipovaccine) was injected by G. L. Scott into perineural tissues and "into the fibrositic areas which seem always to be associated with neuritis of this type", of 15 patients 12 were rapidly "cured", two were "benefited", one was not.

Epidural injections of normal saline through the sacral hiatus seemed to Wallace to be "far the best treatment for chronic sciatica" (No results were given). Subarachnoid injections of alcohol were used by Goff to relieve "sciatic neuralgia". Although there is some danger of motor depression and paralysis, this rarely results, according to Goff, because motor nerves are myelinated and well protected, offering great resistance to the caustic action of alcohol. Of 20 patients with "intractable pain" so treated 15 were "relieved at once", the other 5 were "relieved the same day". A few had a return of pain within the first two weeks but at the end of three weeks 18 of 20 were "entirely relieved". Eight had temporary urinary retention.

(We believe that such injections are not without danger except when done by experts, they constitute symptomatic treatment only and should only be done under special circumstances in cases unrelieved otherwise—Ed.)

Bee venom gave relief in some of Mackenna's cases of "sciatic neuritis" (Very meager details were given). Taylor-Pergalley recommended "labile diathermy"—one electrode kept in motion over the area treated.

Manipulation may bring dramatic relief in certain cases of secondary or central sciatica.^{150, 341} Lewin described indications and methods in detail. Ober gave further results from his treatment of sciatica by incision of contracted iliotibial bands and fasciae. A new skin incision was used. Forty-two patients were treated. 23 were cured, 10 were improved, 9 not improved. A few noted relief "at operation". The majority noted relief of sciatic pain beginning the fifth to the tenth day after operation. "The lame back clears up in from six weeks to six or eight months but occasionally lasts longer". The rationale of the procedure was given. Shortening of the iliotibial band and its fascial expansion causes an abduction contracture of the femur, "resulting in a tremendous leverage action on sacroiliac and lumbosacral joints. Any contracture of the fascia lata must exert muscular pressure on the sciatic nerve which lies beneath the gluteus maximus where it emerges below the piriformis". According to Ober many cases of lumbosacral, sacro-iliac and sciatic pain are so caused. Nutter noted relief

in several cases in which the nerve was explored and iliotibial bands sectioned. The mechanism of relief was uncertain because in some cases tight bands were not found and no irritation of the nerve trunk was seen although relief was obtained. According to Cave "it is the correct diagnosis of iliotibial contracture and not the Ober operation that is difficult." Diagnostic tests were described. Results of fasciotomy in six cases were two cures, two "fair results," one "poor result," one "failure." Of 32 patients treated by a colleague of Ober, results were "perfect" in 27 per cent, "good" in 34 per cent, poor in 39 per cent.

COMMON TYPES OF SPONDYLITIS

Two clinical types were recognized, corresponding to two distinct pathologic types (1) atrophic spondylitis, (2) hypertrophic spondylitis. "Atrophic spondylitis" is synonymous with "rheumatoid spondylitis," and "spondylitis ankylopoietica" or "ankylosing spondylitis." Most current writers were unwilling to subdivide atrophic spondylitis further and considered the so-called subvarieties (a, spondylitis ossificans ligamentosa or Marie-Strumpell type, b, spondylitis muscularis or von Bechterew type) minor variations of one disease. Hypertrophic spondylitis is synonymous with osteo-arthritis of the spine, spondylitis osteo-arthritis.

Details of the clinical, radiologic and pathologic differences of these two main types (and of the subvarieties of the first type) were given in the second review and have been given again ^{203 269 505, 535}

Atrophic spondylitis generally appears in men below 40 years of age, exhibits an increased sedimentation rate and other nonspecific signs of an infection, involves sacro-iliacs early, and stiffens the spine chiefly by a process of ligamentous calcification. Hypertrophic spondylitis generally appears after the age of 45 years in either sex, is not associated with the chemistry of infection, does not involve sacro-iliacs early or characteristically (although they may be affected), produces moderate stiffening by formation of osteophytes which only occasionally coalesce to form isolated bridging, not diffuse regions of ankylosis.

Egyptian mummies exhibited only atrophic arthritis according to some (Jones, 1907 and 1908, Smith and Jones), both atrophic and hypertrophic arthritis according to others (Moodie, 1923, Ruffer, 1926). Shore's examination of spines of predynastic Egyptians would indicate that several types of spondylitis were extant, tuberculous, possibly staphylococcal and other definitely microbic types, also atrophic and hypertrophic types. One, perhaps two, of his seven specimens showed ossification of perivertebral fibrous sheath. Specimens of localized and generalized hypertrophic spondylitis were noted.

ATROPHIC SPONDYLITIS

Three views were expressed that atrophic spondylitis (rhizomelique) is (1) identical with atrophic arthritis elsewhere and is merely atrophic arthritis in the spine ^{505 535}, (2) a separate disease but "somewhat like" or

"having much in common with," atrophic arthritis^{58, 203}, (3) not one disease but a pathologic end result of several diseases^{83, 369}. Much like atrophic arthritis elsewhere, according to Buckley and Golding, atrophic spondylitis differs from the former in several particulars: ligamentous calcification extending some distance from joints as seen in spine, rib articulations and hip joints, is not a feature of atrophic arthritis, the age and sex incidence of the two are dissimilar, the spine is involved seldom in atrophic arthritis, and the small joints rarely in spondylitis, remissions are much commoner in spondylitis than in atrophic arthritis. Miller³⁶⁸ viewed atrophic spondylitis as a pathologic but not a clinical entity. "Ankylosing spondylitis is infective in character and, unlike rheumatoid arthritis of extremities, may be produced by a variety of microorganisms, and develop as a complication of various diseases, such as rheumatoid arthritis, gonorrhea, typhoid fever, bacillary dysentery and influenza, one case has been reported after undulant fever. Without regard to the nature of the infective agent, the pathologic changes are identical." Again he wrote³⁶⁹ "one must bear in mind that in only a small percentage of cases is spondylitis ankylopoietica due to the infection responsible for rheumatoid arthritis. The gonococcus is responsible in a large percentage of cases." The usual absence of streptococcal agglutinins suggested to Cecil that "spondylitis deformans is not always referable to the streptococcus, this would fit in with our clinical observations, for one sometimes sees this form of arthritis coming on after gonorrhea or even after typhoid fever."

(We cannot accept the view of Miller and Cecil. Admitting that the cause of atrophic spondylitis is unknown, we know of no proved cases of gonorrheal or typhoid spondylitis with the chronic clinical course and pathologic reactions of atrophic (ankylosing) spondylitis. Proved cases of gonorrheal arthritis are not chronic and progressive but practically always acute or subacute in onset and course. Typhoid fever produces a localized spinal abscess with resultant localized hypertrophic reaction. The reported manifestations of undulant fever in the spine have not resembled the clinical or pathologic features of chronic atrophic spondylitis—Ed.)

A new series of 124 cases (106 males, 18 females) was studied by Golding. The disease was not more common in manual than in the sedentary workers, 73 per cent of these patients led sedentary lives. Many were free of foci of infection. Blood calcium was high normal. Only nine patients gave a history of gonorrhea. In early cases with sacro-iliac changes only, sedimentation rates were generally elevated (5 to 123 mm) but on the average not as high as in those with sacro-iliac and spinal radiologic changes in which rates were 9 to 110 mm. Golding and Scott repeated Scott's ideas on pathogenesis. All of Scott's 110 cases and of Golding's 124 cases (they may have been overlapping cases as the two writers collaborated) showed radiographic indication of bilateral "infection" of both sacro-iliac joints ("sacro-ilitis") usually with ankylosis. These changes were regarded as long antedating any spinal involvement. According to Scott and Golding the sacro-ilitis generally commences several years before

any symptoms referable to the back or even to the sacro-iliac joints themselves, and has "not therefore been clinically recognized as a manifestation of spondylitis adolescens" (Scott's term for the disease) The patient's course is presumably as follows He develops vague spells or more definite attacks of "wandering pains" across shoulders, down arms, round the ribs, and finally down the thighs, pains of a fibrositic character recurring over several years with free intervals This is the "pre-spondylitic phase," the pains of which are referred to muscles or near joints and are occasionally associated with a resolving synovitis of peripheral joints There may be "tightness of chest" and (according to Golding) pains in thighs and buttocks "Pain in the back or sacro-iliac region is not present at this period" ⁴⁷⁸ Presumably the patient is insidiously developing sacro-ilitis which is apparently relatively symptomless until the disease is well advanced It may cease any time and spondylitis never develop, or it may progress No spinal symptoms (rigidity, pain) are complained of until sacro-iliac ankylosis has already begun Of Golding's 124 patients, 33 presented sacro-ilitis alone, 91 had spondylitis with advanced sacro-ilitis Scott therefore regarded the sacro-ilitis the source of the spinal infection "If this source of infection can be removed or adequately dealt with, spondylitis in the young adult will cease to exist" In three early cases of sacro-ilitis trephining was done pus was absent, cultures were contaminated, the bone was grossly diseased, the operation "certainly proved beneficial" Scott recommended more conservative therapy—wide field radiation with roentgen-rays of medium length Results were "so encouraging that the method is being adopted in all cases seen early enough" Several patients so treated were free of symptoms, one for five years

Weil also held that the fibroid calcification (ligamentous ossification) is a defensive affair secondary to sacro-iliac arthritis and arthritis of the posterior vertebral articulations It is possible, "by recognizing and treating this arthritis in the early stages, to prevent the development of its subsequent lesions, and to reduce or do away with the painful invalidity resulting from it" Prevention and early recognition, according to Scott, necessitate an early radiographic examination of sacro-iliacs "in every case where recurrent attacks of muscular rheumatism extending over a number of years, occur in the young adult"

(Scott has not yet proved his hypothesis Even were the sacro-ilitis the "focus of infection" for the spine, which is not proved, what is the source of the sacro-iliac "infection," by what means does it spread to the spine? So far its infectious nature is only a fairly logical presumption Even were one to discover the early lesion it has not been shown that the therapy of Scott, Weil or any other will consistently check it Final results of Scott's therapy after five years or more will be awaited with interest Others have noted early and frequent involvement of sacro-iliacs in atrophic spondylitis but have not considered it the consistent etiologic precursor of spondylitis In their study of 11 cases of at least two years' duration each, Taylor, Ferguson, Kasabach and Dawson noted calcification of spinal ligaments and ankylosis of intervertebral facets in 100 per cent, the latter was "almost

invariably" (but not invariably) accompanied by sacro-iliac obliteration. Some of us do not recall seeing a case of atrophic spondylitis with radiographically normal sacro-iliacs. Others of us believe that cases of undoubted atrophic spondylitis with radiographically normal sacro-iliacs are occasionally seen. One of us, J. A. K., examined two skeletons with typical spinal ankyloses from atrophic spondylitis in which sacro-iliacs were not involved—Ed.)

Pathology Miller noted one of the reasons for the unusual pathologic reactions of atrophic spondylitis as compared to atrophic arthritis elsewhere in the latter situations the disease first involves synovia. Since intervertebral disks do not have synovia, atrophic arthritis cannot reproduce in disks (the big "joints" of the spine) the same pathologic reaction it produces in peripheral joints. However, as the disease attacks the "true joints of the spine" (the facets or articulations of the transverse processes, which possess synovia), the same pathologic reactions are presumably produced here as in peripheral joints. (Studies on the pathologic reactions in the true joints of the spine in spondylitis are needed—Ed.)

Treatment Scott's treatment was noted. Others advised the usual treatment as for atrophic arthritis elsewhere with certain additions: extra rest in bed on a proper bed in a proper position, breathing and other exercises, plaster shells and braces to prevent and correct deformity. Without giving results, Buckley recommended Ponndorf's vaccine B, roentgen-ray therapy, and gold. Baker considered gold useless. The usual physiotherapeutic methods were advised. Speeding regarded short-wave therapy dubiously. Histamine by injection¹⁵⁷ or by ionization³⁶⁰ was recommended for analgesia. Stecher's six patients received 19 fever treatments with considerable analgesia but no increased mobility. Improvement had lasted one year in one case, six months in five cases. Hartung recommended paravertebral injections of procaine or alcohol, or epidural injections for root pains which some considered common,³⁶⁹ others rare.⁵⁹

HYPERTROPHIC SPONDYLITIS

A localized hypertrophic spondylitis may be the pathologic or radiologic end-result of several causes: trauma, typhoid, undulant fever, or other infection. In the clinical sense, "hypertrophic arthritis" is an entity synonymous with hypertrophic arthritis elsewhere. We²⁴⁷ previously gave a detailed account of the relationship between degenerative changes in the intervertebral disks and hypertrophic spondylitis. Miller summarized this relationship developed by Schmorl and others. The disease is the result of primary degenerative and secondary hypertrophic reactions due to the wear and tear of traction and trauma.^{58, 369}

Considerable attention is being paid to its neurologic manifestations. Some³⁶⁹ are "very positive" that root pains are not directly due to osteophytes. However, the generally accepted cause of root pains is that nerve roots are pressed on by osteophytes in the spinal canal or at the point of emergence from the foramina.⁵⁹ Such a radiculitis was present in 30 cases

of cervical hypertrophic arthritis reported by Hanflig. Pain and other sensory, and sometimes motor, disturbances were produced most often about the shoulder girdle, less commonly at the back or side of the neck and down the arm, occasionally in the precordial region. Hanflig's patients complained of pain of variable severity, sometimes "agonizing," sometimes numbness and weakness of hand, muscle incoordination, at times some muscle atrophy, loss of position sense, even absent reflexes and flaccid paralysis. Varying degrees of muscle spasm and cervical rigidity were noted and rotation of the neck often sharply accentuated the complaints. The cases were frequently misdiagnosed arthritis of shoulder, bursitis, toxic neuritis. In every case cervical hypertrophic arthritis was present and shoulder joints were negative. In each case nerve symptoms corresponded to the cervical segment involved with osteophytes.

The variability and type of pain can be understood from the following. The fourth cervical segment supplies the sensory innervation over the top of the shoulder, the fifth supplies the sensory innervation of the outer surface of the arm between the shoulder and elbow. The deltoid muscle is supplied by nerve fibers derived from the fifth and sixth cervical segments. The pectoralis major and minor are innervated by the medial anterior thoracic nerves (which come from the eighth cervical and first thoracic spinal segments) and the lateral anterior thoracic nerve (from the sixth and seventh cervical segments). Although the latter two are motor nerves and do not carry skin sensory fibers, they can possess protopathic sensations, so that irritation of them may produce diffuse yet definite pain referred to the terminal portion of the nerve. When the anterior roots of spinal nerves are sufficiently involved, there may even be muscle incoordination, loss of position sense, absent reflexes or flaccid paralysis.

The same symptoms which Hanflig noted in cervical hypertrophic arthritis were noted by Turner and Oppenheimer in 50 cases with narrowed cervical intervertebral disks (the precursor of hypertrophic changes) whether cervical hypertrophic arthritis was present or not. Chief complaints were pain in some part of the shoulder girdle, neck, arm, hand, back or precordium, occasionally weakness or inability to perform certain movements (writing, combing hair, fastening buttons, grasping or steering automobile wheel, elevating hand above head "as in the Fascist salute"). Some complained of tingling fingers, pain on turning neck, or on walking or riding, sometimes inability to sleep because of pain in the recumbent position. Others complained of precordial pain—"angina" or "aortitis." Unlike Hanflig's patients (with later pathologic changes), these patients generally had no pain in the neck or definite limitation of neck motion, their commonest complaint was unilateral shoulder pain. Atrophy of small muscles of the hand was sometimes noted. Neurologic symptoms invariably coincided with the cervical region involved in the narrowed disk with or without hypertrophic arthritis. Oblique radiographic views (illustrated) showed actual narrowing of intervertebral foramina even when narrowed disks were present without hypertrophic arthritis.

Because of these experiences, Hanflig, and Turner and Oppenheimer rec-

ommended special clinical and radiographic examination of cervical spines in cases of unexplained shoulder and arm pains and of "angina" without evidence of cardiac disease. Although osteophytic changes are commonly seen on the anterior and lateral aspects of cervical vertebrae they are rarely found on the posterior aspect. Morton demonstrated the latter in three cases which showed that hypertrophic processes can develop posteriorly, and whether posterior or lateral, can extend into the spinal canal and press on the cord, or encroach on the cervical foramina and cause symptoms. Morton demonstrated the posterior projections clearly in oblique roentgenograms. Two of his three patients had pains in one or both arms, hand and neck. One had numbness and tingling of extremities, uncertainty in walking and girdle sensations accentuated by cervical hyperextension. A subarachnoid block was present. The projection was found at laminectomy, after which the patient was "considerably improved."

Treatment Treatment used in Hanflig's cases included a special type of stretching and manipulation. The patient was gently and carefully "hung" by his neck supported in a Sayre's sling suspension with block and tackle. Suspension was repeated for a few seconds each session and two or three sessions were given daily, usually only for a few days. At times, hot fomentations were given and a Thomas collar was worn between sessions. Results were often dramatic, severe pain disappearing immediately while the patient was suspended, returning thereafter but rather rapidly disappearing under continued treatment, usually within 10 to 21 days. Turner and Oppenheimer also noted marked relief with this method which was much easier than manual traction. Ultra short-wave therapy relieved a few, as did soft rubber soles and heels in mild cases. For usual cases of hypertrophic spondylitis short-wave therapy seemed valueless to Speeding. Gold was useless.¹⁸ Histamine ionization reputedly gave analgesia.⁹⁶

GOUT AND GOUTY ARTHRITIS

Gout was called a "forgotten disease."²⁶¹ Current statistics on its incidence foster contradictions that it is rare or that it is fairly common. Pringle found the incidence rising in some English and continental hospitals, falling in others. At the Philadelphia General Hospital a diagnosis of gout was made on only 47 of 414,296 patients admitted in 25 years (1905 to 1929), an average of less than two cases a year, but between 1929 and 1935 it was made on 30 of 146,992 patients.⁹¹ Cohen saw 40 cases the past 5 years. According to Schnitker, only 55 cases of "true gout" were admitted to the Peter Bent Brigham Hospital, Boston, between 1913 and 1935. Only five cases of gout were seen at the arthritis clinic of the Presbyterian Hospital, New York, in 1935, in the same period Herrick and Tyson saw six cases in private practice. Such statistics do not give an accurate index of the situation because the requirements of different physicians for a diagnosis of gout differ so materially. Hench stated that only one of

four or five cases of gout is correctly diagnosed in its early stages. But in some quarters, where physicians are loose with a diagnosis of gout, only one of two or three patients who receive such a diagnosis actually had the disease. In Hench's 100 cases of gout an average of 15 years had elapsed from the first attack of gouty arthritis to the first diagnosis of gout. "The necessity of taking 1500 years to diagnose 100 cases of classical gout does not indicate a proper understanding of this disease."

The features of classical gout were reviewed by several (Cohen, Hench, Herrick, and Tyson, Kersley, Pringle). In diagrammatic fashion, Hench described the basic pattern of gouty arthritis in relation to the appearing time of the four reported features of gout (podagra, hyperuricemia, tophi, punched-out areas in roentgenograms). He divided the course of gouty arthritis into two stages, each consisting of two phases. Stage I is that of acute, recurrent gouty arthritis with complete remissions (phase 1 is that of early attacks, phase 2 that of later, acute attacks with remissions and when hyperuricemia is more established and discoverable). Stage I lasts 3 to 42 (av 12) years. Stage II is that of chronic gouty arthritis (phase 3 is that of early chronic gouty arthritis with acute exacerbations but incomplete remissions, phase 4 the final, relatively symptomless, chronic gouty arthritis).

Discussing criteria for diagnosis of gout Hench noted 20 points expressed axiomatically

These were: Suspect gout when acute arthritis suddenly develops (1) after relatively trivial trauma, (2) after dietary excesses of holidays, birthdays, lodge-night, (3) after any surgical operation ("Acute postoperative arthritis is generally gouty"), (4) after the trauma, exposure and dietary insults of a fishing or hunting trip, (5) in spring or fall (gout has a definite seasonal incidence), (6) in the night between 2 and 7 a.m. (it may occur any hour, however), (7) in patients under certain coincidental treatments such as liver diet for pernicious anemia, ketogenic diet for bacilluria, salyrgan for dropsy, ergotamine tartrate (gynergen) for migraine, insulin for diabetes, (8) acute arthritis occurring in patients with polycythemia or leukemia is usually gouty, (9) to diagnose gout in females requires extra caution. 98 per cent of provable gout is in males, (10) gout is the commonest form of acute arthritis in men over 40 years, it may occur in youth, (11) suspect gout when acute arthritis comes on with dramatic speed, within a few minutes or hours, (12) when the pain is unusually severe, "the worst ever", (13) when the great toe is acutely, not chronically, involved, however, podagra may occur late or never in the disease. (14) when the maximal tenderness is at the mesial aspect rather than underneath or on top of the "bunion joint", (15) the appearance of an involved foot is suggestive (warm, bluish-red rather than cold and bluish-white as in atrophic arthritis), with edema and later desquamation of skin, (16) an acute arthritis of short duration (one to three) weeks and with full restitution of function should make one suspect gout, (17) any case with acute recurrent attacks of arthritis and complete remissions, possibly chronic arthritis later, should invite a diagnosis of gout, (18) since olecranon bursitis is several times commoner in gout than in any other disease, suspect gout in patients who have or give a (sought-for) history thereof, (19) suspect gout in patients with acute or chronic arthritis who have or have had chronic nephritis or renal colic (urate stones or gravel which incidentally cast no roentgenographic

shadow), (20) podagra is a common but not inevitable feature, hyperuricemia, 'characteristic' roentgenographic changes, and tophi are not early but rather late features of gout. Therefore in a case presenting a number of the features listed above one must not hesitate to entertain a diagnosis of gout in the absence of the four most characteristic features.

Some of these points were stressed by others also. Campbell noted the potency of trivial trauma as a provocative. Many stressed, but others minimized, the provocative nature of dietary excesses. One of Cohen's patients developed an attack after alveolectomy, another attack two days after appendectomy. Another patient noted an attack after tonsillectomy. Two of Herrick and Tyson's six patients were women who were taking liver extract orally, one for "a skin condition," the other for an unstated reason. Burchell reported a case of pernicious anemia with uric acid deposits in renal collecting tubules. No history of gouty arthritis was given, the patient suddenly died some time after stopping the use of liver extract in favor of ventriculin. Herrick and Tyson stressed the diagnostic importance of (1) the pattern of gouty arthritis, its recurrence with complete remissions, (2) a therapeutic test with colchicine. According to Graves (1863) gouty patients tend to grind their teeth and produce "bevelled teeth." "Graves' sign" was mentioned by Pringle, Finkle and Kersley, the last considered it by no means diagnostic and not always present. "Coates' sign," defined by Kersley as radial, by Pringle as ulnar, deviation of the terminal phalanx of the little finger, was mentioned. (One of us, P. S. H., has not noted Graves' or Coates' sign as a feature of gout in a study of several hundred cases of tophaceous and pretophaceous gout.—Ed.)

Clinical features of 84 cases were recorded by Cohen. There was a notable incidence among Philadelphia policemen and firemen. Eapen noted chronic advanced tophaceous gout in a Chinese male. Kendall, Fortner and Livingston noted a patient with a painful stump, the leg having been amputated for epithelioma. Later the stump became too painful for an artificial limb to be worn. From the stump a small nodule was excised, it contained scar tissue and giant cells. Within the cells, but not elsewhere, were "uric acid crystals." A diagnosis of gout was made thereon and also because the blood uric acid was 7.2 mg per 100 c.c. and the "usual medical treatment" for gout was followed by relief of symptoms.

(This case may have been one of gout. However, it is difficult for the reader to accept such a diagnosis without reservations. Crystals were identified only on their appearance, no murexide test was mentioned. There was no history of acute arthritis or other feature of gout. The presence of the crystals only within giant cells is an unusual feature, possibly due, as stated, to their destruction by the fixative used. The case is interesting and unique.—Ed.)

Of the 55 patients studied by Schmitzer and Richter, 17 (31 per cent) had clinical nephritis, of the vascular type in 15, and of the glomerular in two (one with nephrosis). Five died in uremia, four were examined post-mortem, three had vascular, one had glomerular, nephritis. Of the 38 pa-

tients without definite nephritis, 16 had albuminuria with little or no renal insufficiency. Compared to control groups, the incidence of hypertension in the 55 cases of gout was high (54 per cent), as was also that of vascular disease (67 per cent). According to Burchell, uric acid is occasionally deposited as free acid in renal tubules of the newborn (uric acid infarcts), or of leukemic adults, it is much more rarely deposited as urates, not free uric acid, in renal interstitial tissue in gout. Thus, interstitial deposition suggests gout, tubular deposition merely suggests hyperuricemia. In gout with leukemia, uric acid is deposited in tubules, urates in interstitial tissue. No renal deposits were mentioned by Schnitker and Richter.

(We understand that a formalin fixative was used. Many valuable specimens of kidneys and joints are spoiled for complete pathologic studies because of this error. Formalin-containing fixatives promptly dissolve urates. Galantha's (1935) method, using absolute alcohol as a fixative, is recommended—Ed.)

Atypical Gout Kersley accepted the following features of "atypical or covert gout"—an articular history very similar to that of atrophic arthritis, supported by a familial history of gout, by Graves' or Coates' sign, perhaps by podagra, hyperuricemia, and radiographic alterations. It is "distinguished with difficulty from the type of rheumatoid arthritis occurring at the climacteric and from certain cases of focal arthritis." Pringle also suggested that perhaps many cases of climacteric arthritis, Heberden's nodes, fibrositis and panniculitis are atypical gout. (We cannot agree—Ed.) Manifestations of the latter, according to Cmunt, include dry eczema and hyperkeratosis of skin and nails, and pretibial edema ("due to irritation of periosteum") frequently seen in patients with hyperuricemia but no arthritis.

(We have seen many cases of tophaceous gout, always with the classical pattern of gouty arthritis, acute attacks, complete remissions, and we practically never have seen or heard of cases of atypical gout which went on to formation of demonstrable tophi. It is impossible for us, therefore, to accept a diagnosis of atypical gout in cases of arthritis chronic from onset—Ed.)

Wood presented four cases of "inflammatory disease in the eye due to gout." The patients had episcleritis periodica fugax. No gouty arthritis or other features of classical gout were present but the patients ate and drank to excess and in two of them the blood uric acid was "greatly increased" (4.6 and 4.1 mg) during the episcleritis and fell later (to 3.5 and 2.3 mg). In one case the disease responded to dietary restrictions. Tiny brown crystals "the size of average bacteria" were noted once in the cornea, and once in the posterior sclerotic. These were assumed to be urates, no chemical identification was possible as they were discovered in fixed specimens.

(The diagnosis of gouty episcleritis remains quite unproved. The illustrated "crystals" do not resemble urates. The therapeutic test was unconvincing. The pathologic reaction noted in the one specimen examined included none of the char-

acteristics of gout (giant cells, and so forth) of other tissues. We are very skeptical about the existence of atypical gout. To our knowledge tophi, the one infallible sign of gout, are practically always absent in such cases. In those very rare cases where tophi are present without arthritis (as yet), one still cannot blame every coincidental disease on gout. In a considerable experience with tophaceous gout we have not seen episcleritis or dermatitis as a feature—Ed.)

Laboratory Data It was generally agreed that hyperuricemia is usually, but not always, present in classical gout, and alone is of limited diagnostic value^{91, 251, 261, 303, 443}. The sedimentation rate is occasionally elevated^{87, 303}. Roentgenograms are generally negative in early cases and are of no help in diagnosis until late in the disease^{201, 261, 443}. Radiographic features in 12 cases were reported without clinical details⁵³⁵. Regardless of what joints may be affected, Scott and Kersley recommended roentgenograms of hands—they may show characteristic changes not seen elsewhere.

(In the experience of one of us, P. S. H., roentgenograms of feet show the characteristic signs earlier than those of hands. In the absence of other data a diagnosis of gout based on the presence of punched-out areas with chronic arthritis is usually erroneous—Ed.)

Pathology The articular pathology was briefly reviewed by Jordan.

Etiology and Pathogenesis Nothing new was presented. Cmunt approved the allergic theory and stated that certain purines seem harmless, but occasionally a purine-free diet, containing a food to which a patient is sensitive, may provoke gout. An 18 year old girl with a serum uric acid of 12 mg developed a "typical gouty attack" after eating a sour gherkin. The aromatic admixture of wine and not its alcoholic content may be harmful according to Cmunt. Uric acid acts as an allergen only in certain cases.

Tophaceous gout with extensive urate deposits on extremities and in joints was produced by Bollman and Schlotthauer in turkeys on a diet of turkey mash plus urea or raw horse flesh but not in those on turkey mash alone or with certain other additions.

Treatment His report on a "history of the treatment of gout" might as well have been titled a "demonstration of the slow progress of medicine," according to Schmitker. About the only things we don't do that the ancients did are "cupping, fancy poultices and pewking." It is particularly unfortunate that gout is so often unrecognized because, as Herrick and Tyson stated, of all the arthritides gouty arthritis can be most readily controlled. Cohen considered treatment highly successful "gout is controllable." The usual therapy was reviewed by several: for the attack, rest in bed, protection for joints, hot compresses, purgation, colchicum, cinchophen or salicylates and alkalies, a diet high in carbohydrates and nonpurine containing proteins, low in fats and free of purines^{91, 222, 261, 297, 303}. It is important to continue certain measures indefinitely after the attack is over. "Interval-treatment" includes purine restrictions, avoidance of alcohol and traumatizing activity, and the intermittent use of certain drugs.

During an attack Herrick and Tyson prescribed colchicine, 1 mg q i d the first day, t i d thereafter until symptoms subsided or diarrhea occurred. Cohen prescribed colchicine 1/120 grain t i d, Kersley used the tincture, 15 minims every three to six hours, with alkali and phenacetin or pyramidon. After the attack, Kersley prescribed cinchophen 75 grains t i d three consecutive days a week for three to four weeks, thereafter once a day three days a week, "with plenty of carbohydrates and calcium." Neocinchophen was used by Herrick and Tyson only for one week after an attack. Cohen's interval-treatment was a purine-low diet and colchicine 1/120 grain t i d one out of every four weeks.

(Cohen admitted that this did not lower the blood uric acid and it would appear that his patients so treated were usually "on the edge" of a gout attack. The pharmacologic effects of colchicine and cinchophen are quite different. Aside from the question of cinchophen toxicity there is no reason why both should not be used during an attack. There seems to be little rationale for continuing colchicine indefinitely, its value is chiefly analgesic, secondarily purgative. For those who are unable to control their gout by diet alone, the intermittent use of cinchophen seems more rational to some of us, but not to W. B., than that of colchicine, which does not affect urate excretion—Ed.)

Histamine injections were used by some, no results were stated.¹⁻⁴⁸¹ "There is probably no disorder so ill-adapted to the injudicious employment of physical methods as [acute] goutiness" (Ray). In intervals between attacks, spa therapy may be of value, however, it may initiate an attack if one is impending (Kersley).

Cinchophen Toxicity No case of cinchophen toxicity in gouty patients was reported. A patient with chronic polyarthritis (type not stated) developed nonfatal subacute yellow atrophy of the liver after taking oxyliodide 0.2 gm q i d for eight days.¹⁴³ Another patient⁴⁸³ had gonorrheal arthritis, he developed nonfatal agranulocytosis without jaundice or hepatitis after taking cinchophen 0.5 gm t i d for about three weeks. Palmer and Woodall reviewed all reported cases of cinchophen toxicity. In 141 (73 per cent) of the 191 cases cinchophen had been taken for "rheumatic diseases" ("arthritis" 70 cases, "rheumatism" 52, sciatica eight, gout six, lumbago four, rheumatic fever one). Of the 191 patients, 88 (46 per cent) died. The actual incidence of fatal and nonfatal cinchophen toxicity is probably much greater than reports would indicate. The vast majority of patients are able to take cinchophen over long periods without injury, but a peculiar susceptibility to it may cause disease or death from large or even small doses. Cinchophen had long been used by some without apparent harm, then jaundice and sudden death occurred. In some cases very small doses were used and withdrawn at the first sign of toxicity, yet death ensued. Palmer and Woodall concluded that there was no safe dosage or method of administration of cinchophen. They doubted the wisdom of its use even in gout which can often be handled "satisfactorily over a period of years without cinchophen." Comfort believed its use was justified in gout since there is no pharmacologic substitute for it in gout, but it should not be used otherwise. Its dangers can be reduced by discontinuing its use permanently not temporarily, at the first sign of toxicity and by strictly avoiding surgery.

procedures on those so affected, otherwise death may result. Cinchophen being "the drug par excellence for gout" (and for certain other patients with arthritis or lumbago "who were living a miserable existence without it") Westfall considered the slight risk worth taking. Of his miscellaneous patients 1589 each had taken from a few up to 4000 tablets (each tablet 0.5 gm). Between 25 and 100 tablets were taken by 886 patients, 250 to 500 tablets by 195, 500 to 1000 tablets by 47, 1000 to 1500 tablets by 11, more than this by 8 or 10, less than 25 tablets by the rest. Several took the drug daily for three to four years. Only one death occurred—a woman with cholecystitis developed acute yellow atrophy. Two others recovered from toxic jaundice, mild gastric symptoms were noted in 89 cases, a rash in eight, hives in five. The great majority noted no symptoms whatever. Westfall recommended that the full daily dose be given at one time, after supper, with a "teaspoonful of soda." It should never be given to a patient with liver damage, gastric distress or one on a restricted carbohydrate diet.

In 1933 Barbour and Fisk produced liver damage in rats by large doses of cinchophen. Recently Barbour, with Gilman was unable to repeat his previous work. With large doses of cinchophen and tolysin they were unable to produce hepatic lesions in rats even after attempts to make the liver more susceptible to cinchophen by starvation diets to deplete liver glycogen or by large doses of fat or alcohol. The growth of rats was unaffected by large doses of tolysin but was affected by cinchophen. The antipyretic effect of tolysin appears early and is short, that of pyramidon is delayed but lasts longer. A combination of the two produces a rapid, prolonged effect with no added toxicity.

Unable to produce liver damage in rabbits or rats from cinchophen alone, Radwin and Lederer noted that cinchophen, in combination with intravenous injections of colon bacilli or streptococci, produced no hepatic lesion not produced by infection alone. Sensitivity of patients to cinchophen is therefore a peculiar one not apparently related to previous or coincident hepatic infection. Peptic ulcers and gastric hypersecretion, but no hepatic or other lesions were produced in dogs given cinchophen by Stalker, Bollman and Mann. Reid and Ivy also produced gastroduodenal ulcers but no hepatitis in 100 per cent of 15 dogs. The administration of gastric mucin markedly prevented such lesions and acute toxicity in 82 per cent of 13 dogs.

Hench (1933 et seq.) and others reported that jaundice from cinchophen, and other types of jaundice, produced a marked reduction in symptoms of patients with atrophic arthritis or primary fibrositis. In Diack's case of polyarthritis with hepatitis and jaundice from oxyiodide the condition of joints during jaundice was not described, it was noted that five months later "arthritic pains still persist to a slight degree." The phenomenon described by Hench is apparently relatively specific for atrophic arthritis and primary fibrositis. Others have described certain types of arthralgia or arthritis coming on after, or even with, hepatitis and jaundice. Sager saw a young

woman with "grippe" followed by febrile polyarthralgia (no swelling). About two months later, without the use of cinchophen, jaundice developed, icterus index 100 bilirubin 7 mg per cent. "With the deepening of the jaundice the severity of the arthralgias had diminished although they never disappeared entirely." Of 208 patients with parenchymatous liver degeneration seen at the Mount Sinai Hospital since 1929, Sager found that 30 (14 per cent) had had "arthritis" or severe arthralgia, of whom 10 had had cinchophen but 20 had not. Cinchophen has been used with great caution since 1932 but Sager's statistics showed that the frequency of arthritis and jaundice did not decrease after 1932. He concluded that certain patients with "arthritis" will develop catarrhal jaundice whether they take cinchophen or not and cinchophen is too often incorrectly blamed for this jaundice.

(In view of the phenomenon noted by Hench and current attempts to reproduce it therapeutically in atrophic arthritis, a more detailed review of these cases by Sager would be of considerable interest. Sager made no attempt to classify arthritis or arthralgias and did not give any time or symptomatic relationships between jaundice and joint disease. Sager called his case of febrile polyarthralgia without swelling "infectious arthritis", it was probably not atrophic arthritis—Ed.)

Uric Acid Problem Studying uric acid clearance tests on two nongouty patients McLester concluded that the renal excretion of uric acid is of the same type as that of urea rather than of the type of creatinine and the non-metabolized sugars. Larson and Chaikoff (1935) showed that injections of insulin or of epinephrine increase the blood and urinary uric acid in Dalmation dogs, the urinary allantoin in other dogs. Larson and Brewer have now shown that insulin affects purine metabolism, not per se but indirectly through epinephrine, insulin hypoglycemia produces an increased secretion of epinephrine from the adrenals.

PSORIATIC ARTHRITIS ARTHROPATHICA PSORIATICA

Psoriasis is common and is frequently seen in patients with all manner of articular complaints. Under the term "psoriatic arthritis," writers have listed cases of psoriasis with rheumatic fever, with atrophic arthritis or with hypertrophic arthritis. The reaction to such an indiscriminate application of the term to such cases, the great majority of which have merely been of psoriasis occurring coincidentally with unrelated joint disease, has been that most rheumatologists refuse to believe there is such an entity. A current example of loose usage follows: "Occasionally in the aged, pain and swelling in the larger joints accompany the [psoriatic] rash. This is the so-called psoriasis arthropathica"¹⁵² Others have used certain clinical and roentgenologic criteria to restrict the term to a special syndrome. The matter was discussed by Shlonsky and Blake, who reported a case of what they believed to be true psoriatic arthritis.

A female aged 57 years had suffered with progressive psoriasis and polyarthritis, both of which began 20 years before. Psoriasis was generalized with coalescent

lesions, nails were thickened, crusted, grooved. Multiple joints, especially those of distal extremities, were involved in a destructive process, with ankylosis in a few joints but with massive bone absorption and the development of "opera glass fingers and toes" ("main en lorgnette") from a veritable dissolution and telescoping of certain joints of wrists, fingers and toes. The patient's serum contained no agglutinins for hemolytic streptococci. The objective and radiographic appearance of the joints was described in detail. Besides osteoporosis and destructive changes, the radiographic feature was a tapered narrowing of articular ends of bones with the production of "ball and socket joints."

(One of us, P S H, has called these "pencil-to-pencil joints" or "pencil-in-cup joints" because the end of one bone is destroyed to resemble not a ball but a dull pencil which may oppose a similarly destroyed bone-end or one presenting the shape of a cup—Ed.)

Shlonsky and Blake considered it a most extensive case of psoriatic arthritis, simulated by only one reported case (Bauer and Vogl, 1931). They believed that the psoriasis and arthritis were etiologically related but were uncertain whether this type of arthritis is peculiar to psoriasis.

(We are divided in our opinion on the specificity of this entity. Some of us (W B, F H) believe that psoriatic arthritis is merely atrophic arthritis and associated psoriasis, this being such a case, and that similar extensive destruction of joints may occur without psoriasis in cases of atrophic arthritis. Others of us (P S H, C H S) regard psoriatic arthritis as an entity, a disease which objectively affects central and less peripheral joints, much as in atrophic arthritis, but which has certain pathognomonic features, chief of which is the proclivity with which it affects the distal joints of fingers and toes in a destructive arthritis in conjunction with psoriasis of nails²⁴⁷. Although psoriatic arthritis is often fairly mild, it may be severe. Hench has seen in severe cases only, the peculiar type of bone destruction and dissolution noted in this case, an appearance which he has never seen exactly duplicated, even in the most severe cases of atrophic arthritis—Ed.)

Ingram noted the "association of rheumatic manifestations [of unstated type] in muscles, nerves and joints" in three of twelve cases of pustular plus "ordinary" psoriasis, but in none of 20 cases of pustular psoriasis without ordinary psoriasis. According to Duckworth, nails are not usually affected in cases of pustular psoriasis.

(In scaly, disseminated or patchy psoriasis, nails are commonly involved and sometimes with them the terminal phalangeal joints—Ed.)

Treatment Most reports on the treatment of psoriasis did not mention joint lesions. Some believe that psoriatic arthritis in its early stages can be largely controlled by vigorous therapy to control the psoriasis. If this is true, treatment of the skin is an important feature of the therapy of psoriatic arthritis. In line with the beneficial effect of summer sunshine on psoriasis, striking improvement in three cases of "notoriously stubborn psoriasis" was noted by Krafka from the use of "massive" (20,000 units daily), later "maintenance" (4000 units daily) doses of vitamin D (haliver oil with viosterol). Small doses were useless. The largest dose was first given in 10 day courses with 10 day rest periods. When the psoriasis had

cleared, the smaller doses were used. Thurmon noted "a decided beneficial effect" from the use of a noncolloidal organic sulfur solution in 70 cases of psoriasis. Colloidal manganese was recommended by Spitz, "psorimangan" by Schwartz. The histopathology of the skin lesions was described,³⁴ and a historical review of psoriasis was published.³² Joints were not mentioned in the five papers last mentioned.

HEMOPHILIC ARTHRITIS

Of 98 patients with hemophilia seen by Thomas, 79 per cent (77 cases) had hemophilic arthritis, 61 per cent (60 cases) had permanent joint deformity. Joints most commonly affected were knees (68 per cent), ankle (56 per cent), elbow (53 per cent), hip (16 per cent), fingers (15 per cent), wrist (5 per cent), spine (3 per cent), toes (2 per cent). Shoulders generally escaped involvement. One case of spinal involvement had been misdiagnosed Pott's disease. One patient had a Volkmann's contracture after extensive hemorrhages in an arm. The patients' ages ranged from the newborn to 65 years. Additional cases of hemophilic arthritis were reported 11 by Timperley, Naish and Clark, one by Sutton. Firor and Woodhall saw an unusual case of a large, hemophilic, pseudotumor of a thumb with destruction of both phalanges and metacarpals. Previously diagnosed bone sarcoma, the unique lesion represented the end stage of traumatic hemophilic hemarthrosis. "The march of events in small bones has never been ascertained roentgenographically." The pathologic results were similar to those which occur in large bones or joints, but instead of regression and eventual ankylosis, progressive destruction and cutaneous rupture may also occur in small bones and joints.

Crandall found reported four doubtful but no certain cases of hemophilia in negroes. Crandall cited "apparently the first instance" of hemophilia and arthritis in a full-blooded negro. Only five cases of Volkmann's contracture in hemophiliacs have been reported, two new cases were seen.^{263, 542}

Roentgenographic and pathologic features²⁴⁵⁻²⁴⁷ of hemophilic arthritis were briefly reviewed.¹⁷⁶

Treatment For joints. This was reviewed by Thomas. Injury to joints must be avoided. Affected joints must be put at rest. In the acute stage, ice bags may lessen pain, reduce swelling, and shorten invalidism. Adequate arterial pressure distal to large hematomas must be insured by blood transfusions if necessary. When contractures have occurred, treatment consists of very slow traction, careful diathermy, gentle massage, carefully applied casts and turnbuckles followed by slow, cautious motion. This may require months during which joints are rested in bed, later, casts, crutches and canes. Firor and Woodhall amputated the thumb affected by the hemophilic pseudotumor safely and rapidly by electrocautery. Normal healing resulted, a remarkable and rather prolonged postoperative reduction

of clotting time from five hours to five minutes occurred, perhaps from some mobilization of thromboplastic substance incident to cauterization

For the hemophilia Having used various ovarian substances, corpus luteum, whole ovary, and so forth, with little effect, De Silva controlled hemorrhages of hemophiliacs and others with theelin

(Data on the cases reported were too meager for one to accept the diagnosis of hemophilia or to approve the conclusion—Ed)

A placental extract markedly reduced the clotting time in 11 of 15 cases seen by Eley and associates. Oral use was more effective than intramuscular use. Timperley, Naish and Clark had "excellent results" from a new mixture of potassium bromide and egg white given intramuscularly or intravenously. It did not produce local or general intravascular clotting but reduced the clotting time of blood and controlled hemorrhage of 13 patients so effectively that they endured with impunity such unusual trauma as pounding with a hammer, jumping from chairs, kicking a football, running over uneven ground, dental extraction, and so on. In testing the method "patients were encouraged not to spare themselves the knocks and cuts which of habit they had avoided." Russell's viper venom, applied locally, controlled dental hemorrhages.^{20 73} In Sutton's case of hemophilic arthritis and epistaxis, the venom used locally and orally was ineffective. Injections of whole parental blood and coagulin were helpful.

Of interest was a study of blood coagulation in hemophilia by Patch and Stetson. (In evaluating therapy it should be remembered that the clotting time of hemophiliacs may vary markedly from day to day or from week to week—Ed)

ALLERGIC, METABOLIC AND ENDOCRINE ARTHRITIS

Though still used by some, these terms are being employed with more caution, they have not yet been accurately defined. Some use the terms to indicate an arthritis presumably different from any other, others consider them more or less synonymous with either atrophic or hypertrophic arthritis. Thus, Pringle wrote, "Though there is not sufficient laboratory or clinical evidence to show that rheumatoid arthritis is a definite disease due to errors in metabolism, clinically I believe that the primary form is metabolic and probably due to some imbalance in the endocrines." Nissen believes that "psychogenic (endocrinal and metabolic) factors" underlie many obscure cases of arthritis. Wootton expressed the belief that arthritis represents food allergy or bacterial allergy in the presence of hyperparathyroidism. "Practically all non-septic joint disturbances begin as an allergic reaction" to bacterial allergens in early life, to food allergens later. But bone changes will not take place unless there is a concomitant hyperparathyroidism.

(This is pure speculation, no proof of any sort was offered—Ed)

Allergic Arthritis The application of the allergic hypothesis to rheumatic fever, atrophic arthritis and gout has been noted. No one has been

able to set up any one articular syndrome as "allergic arthritis" or to prove that any of the arthritides are chiefly or solely the result of bacterial or food allergy. Young noted that patients with atrophic arthritis are susceptible to skin allergy but not especially to hay fever or asthma. But patients with such allergy rarely had arthritis. He believed that atrophic arthritis might represent a bacterial allergy but concluded from skin and diet tests that food allergy played no role. Some rheumatism specialists consider intermittent hydrops the nearest approach (aside from serum sickness) to an "allergic arthritis." Supporting this view, Lewin and Taub presented a case of "allergic synovitis due to ingestion of English walnuts."

A boy, aged 16, had intermittent (every two to three months) stiffness and swelling of knees for 10 years, attacks lasting 24 hours. His parents had hay fever, and urticaria from strawberries and tomatoes, he did not. A typical attack in knees was induced within 72 hours of eating the meats of half a pound of English walnuts. Skin tests were positive to English walnuts only. Subsequent provocative and therapeutic tests were positive.

"Metabolic Arthritis" Aside from applying this term obliquely to atrophic or hypertrophic arthritis and more directly to gout, current writers failed to stress, or clarify it further.

Endocrine Arthritis The idea that endocrine disturbances may act as predisposing or aggravating factors in atrophic or hypertrophic arthritis is admitted by many rheumatologists and emphasized by a few. But this is a different matter from saying that a certain type of arthritis is due solely to the overfunction or underfunctioning of one particular endocrine gland, in which case a true endocrine arthritis would exist (and not, for example, an infectious arthritis modified by endocrine factors). Ellman and O'Brien accepted a relationship between hypertrophic arthritis and "endocrine imbalance," presumably an ovarian deficiency with or without hypothyroidism or frank myxedema. "A lowered basal metabolism occurs in a noticeably large number of these patients."

(But for hypertrophic arthritis to be a true endocrine arthritis due to hypothyroidism, a lowered rate must *always* be present, which it certainly is not—Ed.)

Finkle argued that arthritis may sometimes occur with myxedema. Others (Schmitker et al.) have noted "chronic arthritis" occasionally in cases of spontaneous myxedema, and muscular pains in patients with induced myxedema (post-thyroidectomy).

(According to Monroe, 1935, myxedematous patients rarely have atrophic, often have hypertrophic, arthritis. The percentage relationship was too low to justify regarding myxedema a primary factor—Ed.)

Peers, studying metabolic rates in various arthritides concluded that "the true arthritic is a nonmyxedematous individual." The low metabolic rates seen fairly often in arthritic patients "are not due to a lack of thyroid hormone but are brought about in some other fashion." Tidy

also concluded that neither hypothyroidism nor hyperthyroidism is the primary cause of any chronic rheumatism, even though thyroid extract may help arthritics with low rates, "there is no reason to ascribe any specific action to thyroid"

"Climacteric Arthritis" This holds a precarious position in the family of arthritides. It is placed in the classification of the Ligue Internationale Contre la Rheumatisme as synonymous with "endocrine, metabolic, hypoglandular rheumatism, villous arthritis, rheumatic gout, gout in women". The classification of the British Medical Association includes "chronic villous arthritis, mainly occurring in women at or about the climacteric". Neither climacteric nor villous arthritis is recognized by the classification of the British Ministry of Health, nor in the official nomenclature of the Royal College of Physicians. Recently a subcommittee of the Royal College of Physicians listed "climacteric arthritis (villous type)" twice, deciding that it may produce either a "rheumatoid type" or an "osteo-arthritic type" of chronic arthritis¹⁷. Thus, three views are held that "climacteric or villous arthritis" does not exist (this view is held by most of us—Ed), that it is an entity with special clinical and pathologic features, or that it is an entity which produces now one, now another pathologic reaction.

Etiology of Climacteric Arthritis Seven writers currently expressed their views thereon. Although the majority believed that climacteric arthritis was due to some kind of endocrine deficiency, they were not certain just what kind. The cause is probably hypothyroidism according to Thomson, who nevertheless prescribed pituitary extract also in some cases. A Court noted the disease in florid stout patients "with signs of thyroid deficiency". Gordon considered it "an endocrine deficiency especially of thyroids". Fox did not incriminate endocrines but considered it due to "disturbances of digestion, metabolism and excretion," to "toxic or metabolic factors" due perhaps to "the formation of abnormal substances or to simple failure of excretion".

(Obviously the above writers were very hazy as to the cause. None gave laboratory data indicating a consistent deficiency of ovarian or thyroid function. It should not be difficult for those who believe in the entity to apply to reputed cases the newer laboratory methods for estimating ovarian and other deficiencies. This would do much to settle the argument—Ed.)

Clinical Aspects of Climacteric Arthritis There was no uniformity in the clinical picture presumably characteristic of "climacteric arthritis". Some regarded it as synovitis, others as arthritis. According to Thomson it "occurs exclusively in middle-aged women, affects the knees and occasionally one or more other joints, such as wrists". It affects knees according to Buckley, knees but also first metacarpal joints according to Gordon. A Court considered it "a gradual increasing stiffness and pain in affected joints, usually the knees". Fox separated "climacteric arthritis" or the "arthritis of middle life" from both atrophic and hypertrophic arthritis.

He regarded it as "different from the much more serious rheumatoid arthritis of the young, on account of its mode of onset and the order in which the joints are affected, its more favorable course, its limitation often to a few joints, and its occurrence in comparatively healthy people" According to him, intermissions of one or two years are not uncommon, after a few years there is comparative quiescence with localization in one or two or a few joints, a "less profound constitutional disturbance, and thus a more favorable prognosis" Incidentally, I have noticed in many cases that the arthritis has been almost or quite confined to the left side of the body" It affects married women, especially those with children, much oftener than the single The average age of onset in Fox's cases was 48 (range, 37 to 54) years

Hall's conception of "menopausal arthritis" was much more inclusive He studied 49 women who developed joint distress coincident with the onset of menopausal symptoms Of the 49 cases, 23 were "castrates" (two by roentgen-ray, 12 by operation, nine by unilateral oophorectomy with subsequent "stormy menopause"), 26 experienced a physiologic menopause Of the castrates, six developed atrophic, four hypertrophic arthritis, 13 "arthralgia" Of the others, 12 developed atrophic, five hypertrophic arthritis, nine arthralgia Thus menopausal arthritis simulated atrophic arthritis in 18 cases, hypertrophic arthritis in nine cases, "arthralgia" in 22 cases Unable to determine concentrations of urinary estrin or prolan A, Hall based his diagnosis of menopausal arthritis on the coincident appearance of menopausal and articular symptoms, but especially on the beneficial effect of estrogenic substances on the former Joints involved, in order of frequency, were hands, knees, neck, wrist, fingers, ankles and lower back In marked cases 25 to 50 per cent of all joints were involved "Arthralgia" consisted of absence of swelling or of marked tenderness, heat, redness, crepitus or altered function, presence of irregular pain, morning stiffness, slight puffiness and tenderness, pains coming and going abruptly, often appearing markedly at night, perhaps due to vascular spasm

Pathology of Climacteric Arthritis According to Thomson and a Court "proliferative synovitis" is primarily present, with fine crepitations audible and palpable on joint motion Fox and Gordon considered it different from, but often ending in, osteo-arthritis "The typical change in the knee joint is a villous overgrowth of the synovial membrane, passing in a few years into a later stage of degenerative osteo-arthritis" Hall's views were noted To Fletcher the pathologic reaction "may be rheumatoid in type, more usually it is villous or osteo-arthritic"

Roentgenographic Changes of Climacteric Arthritis These were not specifically defined Scott found no radiologic picture characteristic of "climacteric arthritis"

(We are divided in our views Most of us do not recognize it as an entity, believing that it is a mild senescent hypertrophic (degenerative) arthritis with or

without its commonly associated fibrositis, or that it is atrophic arthritis in a patient at the menopause. Its supposed pathology of primary and dominant synovitis, later associated with degenerative changes, presents a hybrid between that of atrophic and hypertrophic arthritis, or else represents a mixture of the two, the synovitis of mild atrophic arthritis coincidentally or subsequently associated with the inevitable degenerative changes of hypertrophic arthritis. Matters could be distinctly clarified if the protagonists of the entity would present pathologic data on "typical cases." Do they present synovial pannus formation, lymphocytic collections characteristic of atrophic arthritis, and the cartilage changes of atrophic arthritis, do they demonstrate the usual picture of hypertrophic arthritis, or do they present a specific and unusual type of synovial and cartilage involvement?—Ed.)

Treatment of Climacteric Arthritis Usual treatment was thyroid extract, weight reduction, correction of posture and flat feet^{118, 181, 546}. Iodine and pituitary extract were recommended⁵⁴⁶. Fox, believing it a metabolic, not an endocrine, disturbance, did not recommend endocrines but general measures to promote elimination and reduce strain. The osteo-arthritic stage can be prevented, according to Gordon. "If properly treated by increasing the local synovial activity, by heat, and other means, and by redressing the endocrine deficiency, especially that of the thyroid, the original arthritic process can be cured before any osteo-arthritis has supervened." Without details Fletcher recommended estrogenic therapy.

Intramuscular injections of theelin or progynon controlled menopausal symptoms in all of Hall's 49 cases. From 50 to 100 per cent of relief in joints was noted in 91 per cent of the 22 cases of arthralgia, 66 per cent of the 18 with atrophic and 44 per cent of the nine with hypertrophic arthritis. Treatment and results differed in the castrates and those with a physiologic menopause. Individual doses varied from 200 to 2000 rat units (1000 to 10,000 International units). Some received 6000 rat units weekly. Relief (50 to 100 per cent) of joints was experienced by 82 per cent of the castrates, by 65 per cent of the others. The former required more than 2000 rat units in oil per week, noncastrates required 2000 rat units or less weekly. Usually at least six doses were necessary, doses being given at five to seven day intervals.

Acromegalic Arthropathia Human "acromegalic arthritis" has been noted (for example, Erdheim, 1931). Silberberg produced its pathologic counterpart in guinea-pigs by injecting an acid extract of cattle anterior pituitary gland. First noted were hypertrophy and hyperplasia of cartilage cells, first in the transitional, later in the sliding and pressure zone. This proliferative process was then followed by liquefaction and degeneration of the growing cartilage, with ulceration of its surface. Calcification of cartilage was later noted. Since similar or greater changes were produced in thyroidectomized guinea-pigs, the pituitary extract obviously acts without intermediation of thyroid.

Arthritis and Parathyroids The arguments of those few physicians who "without good evidence" attempted to relate arthritis to hyperparathyroidism have been about silenced. Wootton argued relationship, not di-

rect but indirect, between various articular diseases and parathyroids. His "commonplace viewpoint" is very hypothetical and fanciful, with absolutely no scientific proof to support it. Reviewing past arguments favoring a relationship, Jessop, Wilder and Howell, Parsons and others agreed that none of the arthritides have any proved connection with hyperparathyroidism. Apparently considering the argument "closed" or fruitless, most current writers on hyperparathyroidism did not even mention joints.

Although the skeletal pathology in clinical hyperparathyroidism is osseous, not articular, it behooves rheumatologists to be familiar with hyperparathyroidism because of its frequent "rheumatic-like" symptoms. The disease characteristically produces skeletal aches and pains particularly in the back (72 per cent).⁷³ The osteoporotic form of the disease (the early stage of the classic type without cysts or bone tumors, when symptoms are produced by generalized decalcification) is often diagnosed "rheumatism." One should suspect hyperparathyroidism in patients with generalized "rheumatic" or "neuritic pains" or with unexplained arthritic pains of the nerve root type,^{53, 333} but *only* if they (repeatedly) exhibit the classical chemical features. In hyperparathyroidism blood calcium and phosphatase and urinary calcium and phosphorus are high, blood phosphorus is low. In chronic atrophic and hypertrophic arthritis the blood and urine calcium and phosphorus are generally normal and blood phosphatase is normal or slightly low.

Several of the recent cases of proved hyperparathyroidism presented "rheumatic" symptoms.

One patient's chief complaint was pain in feet, legs and back, seemingly affected by weather, and the condition was treated as "rheumatism" for six months.⁶⁸ Another had weakness and severe pains in arms, lumbar region and legs called "sacro-iliac strain and sciatica."¹⁷ The aches and pains of one had been called "arthritis", another had pain and tenderness of a sacro-iliac joint, limited motion of spine and a tender hip.⁸⁶ One case of severe pain in neck, back, and both legs was labelled "neuritis" for eight years.²³³

Others noted pains in back and shoulders on motion,^{283, 436} but specifically stated that the pains were not in joints. In three cases of Merritt and Lattman, articular complaints were noted: one patient had a painful swollen knee with cystic bone destruction at the distal end of the femur; another had a painful shoulder, hip and back; the third had painful, tender hands, forearms and shoulders called "chronic arthritis" by a leading rheumatologist.

(We cannot be sure that these three cases were of hyperparathyroidism. Chemical studies were incomplete or not done, biopsy was not made, the patients were treated by roentgenotherapy.—Ed.)

Injectations of parathormone in rats produced osseous and other lesions characteristic of clinical hyperparathyroidism but no articular lesions (Johnson, 1932). Animals fed large doses of vitamin D will also develop similar osseous changes and metastatic calcification. In addition to these, however, Fang and Miltner noted degeneration and calcification in articular cartilage and intervertebral disks (lesions not noted in clinical hyperparathyroidism). The lesions disappeared after administration of vitamin D was stopped.

For those interested in the general subject, its clinical types, chemical and radiologic differentiation, urologic features, complications and treatment, several other excellent reports are available, in particular, Wilder and Howell's summary of 135 reported "proved cases" ^{42, 71, 201, 212, 268, 304, 378, 386, 411, 412, 426, 456}

Chemical "Arthritis" or Arthralgia Arthritic patients receiving thyroid extract sometimes note increased joint symptoms, presumably due to heightened sensitivity and lowered threshold for pain. However, nonarthritic patients with myxedema, or with low basal rates without myxedema, commonly develop generalized arthralgia and particularly myalgia (influenza-like) for a few days shortly after starting thyroid therapy (Plummer and Boothby, 1927). One of the toxic manifestations of excess alkali therapy for duodenal ulcer is aching pain ("grippe-like") in muscles and joints (Hardt and Rivers, 1923). Such forms of toxic myalgia and arthralgia might be designated myalgia or arthralgia medicamentosa. Genner has used the term "paratherapeutic articular disturbance" to indicate articular symptoms from antisyphilitic treatment. Of 2235 patients under such therapy, 79 (3.5 per cent) developed articular disturbances, usually polyarticular, generally only arthralgia, occasionally with slight swelling and redness. Symptoms sometimes lasted months after therapy was stopped. In two cases severe arthralgia necessitated hospitalization. Bismuth, not arsphenamine, was held generally responsible. Of patients with arthralgia, 42 per cent were receiving bismuth alone, 54 per cent arsphenamine and bismuth, and only 4 per cent arsphenamine alone. Common signs of bismuth intoxication were jaundice (116 cases) and erythema (148 cases). Although jaundice and arthralgia usually did not occur together, the combination was noted in 10 cases, jaundice appearing before the pain in three, after the pain in seven cases.

(No note was made on intensity of jaundice or any ameliorating effect of this type of jaundice on joint pain—Ed.)

Wolf (1925) believed the arthralgia was caused not by a direct toxic effect of the medicine on joints but by an indirect effect through impairment of hepatic function, so that noxious autolytic products enter the blood stream and produce, among other effects, articular pain. Genner favored a "direct toxic-medicamental effect" in spite of the frequency of hepatic symptoms. "The individual tolerance is dependent on the detoxicating power of the organism (largely dependent on hepatic function) and on the functional capacity of excretory organs. When these safety valves fail to work properly, toxic by-effects appear."

MISCELLANEOUS TYPES OF JOINT DISEASE

Synovitis, Transitory Synovitis of Hip Joints Children under eight years of age are affected. Finder saw 22 cases subsequent to 1916. Symptoms were a limp, pain frequently referred to knees, night cries, restlessness,

often slight fever and leukocytosis. Since synovia alone was involved, roentgenograms were negative. Presumed causes were trauma and infection. Treatment included rest, traction, sometimes immobilization, physical therapy. "The outcome is uniformly good."

(May these not be cases of atypical atrophic arthritis?—Ed.)

Tenosynovitis Spencer reviewed features of the traumatic, suppurative, gonorrheal, syphilitic, tuberculous, and "rheumatic" types. Early and adequate incision is necessary in synovial whitlow (suppurative tenosynovitis).⁴⁶⁰ Cohen's patient with "tenosynovitis crepitans" of a wrist, precipitated by trauma, unrelieved by rest and physical therapy, had oxaluria and had had an oxalate renal stone. Measures to stop oxaluria (special diet and medicines) relieved wrist pain within three weeks. Six other patients responded similarly. Patients refused biopsy. Cohen recommended metabolic studies and this treatment in similar cases.

Stenosing Tendovaginitis DeQuervain's Disease Occupational trauma produces "snapping thumb or finger" caused by a localized thickening of the tendon as it passes with effort through a partially stenosed tendon sheath. Tendons themselves are usually normal. Although not uncommon, only 200 cases have been reported. Thirty-five new cases were noted (Burns and Ellis, Patterson, Zelle and Schnepf). A thumb is usually affected, with slight swelling and marked tenderness over the radial styloid. Voluntary abduction or forcible adduction of the thumb is painful. Conservative treatment is generally unsuccessful. "Immediate relief" is obtained by simple incision of the constricting sheath.

Intermittent Hydrarthrosis It is uncertain whether this is a pathologic, or a peculiar physiologic, reaction of the articular lining or of those elements which produce synovial fluid. Pathologic reactions in one case were slight thickening of the lining layer of cells without increased fibrosis or perivascular thickening (Ghormley and Deacon). In Collin's case the total synovial cell count was 1600 per cu. mm. in one knee, 2500 in the other with 58 and 71 per cent polymorphonuclears.

Synoviomas Black described a benign synovioma arising from a tendon sheath or bursa of a hand following injury. Its cells produced a mucinous fluid resembling synovial fluid. Early symptoms of malignant synoviomas may resemble those of "arthritis." Synovial sarcomas are rare. Knox reported 19 cases from the literature and three new ones. Knee joints were affected nine times. First symptoms were swelling, tenderness and pain, usually before, occasionally after, the appearance of a mass. They rarely arose in arthritic joints. Malignant tumors of joints, bursae or tendons are fibrosarcomas or synovial sarcomas. The latter are resistant to radiation, not cured by amputation.

Chondromas These were classified by Moore as (1) simple ecchondroma, enchondroma, (2) compound osteo-, fibro-, myo-, angio-, papillary-chondroma, (3) malignant chondrosarcoma. Simple or malignant second-

ary changes may develop, in order of frequency calcification, ossification, fatty degeneration, mucoid softening, cystic degeneration, surface ulceration, sarcomatous degeneration, chondroma-sarcoma Baker discussed osteochondromas, the commoner type A case of chondroma of the head of the fibula, described by Moore, was regarded most unusual because "few parts of the skeleton are so seldom the site of pathologic affections and anomalies as the proximal end of the fibula" Multiple loose bodies in joints most often arise from synovial osteochondromatosis, a metamorphosis of synovial membrane into a benign tumor^{194, 195}

Hypertrophic Pulmonary-Osteo-Arthropathy A case with usual features was seen by Kline, the patient was a boy with pulmonary tuberculosis

Arthritis and Scleroderma A child developed cicatrizing morphea (circumscribed scleroderma) over buttocks, legs, abdomen A few months later pain and tenderness involved knees, hips and ankles without swelling or inflammation Ankylosis of hips, flexion of knees, stiffness of feet, bone atrophy and calcium deposits in patellar ligaments and Achilles' tendon ensued (Crawford)

Supratiotchanteric Calcification Calcified deposits near the greater trochanter may cause pain and disability of a hip Such deposits were found by Goldenberg and Levinthal in none of 100 patients under 15 years of age, in 30 (5.4 per cent) of 550 patients over 15 years, 20 affected the gluteus medius tendon, eight the bursa between the tendon of the gluteus medius and the greater trochanter, two the under surface of the gluteus medius Reflex spasm of the latter limited abduction and internal rotation of the hip The condition is analogous to that affecting the supraspinatus muscle in "sub-acromial bursitis" Surgical removal of deposits provides a cure

Miscellaneous Conditions Conditions which give rise to symptoms which imitate arthritis were discussed by Kerr syphilitic dactylitis, bursitis, myositis or periostitis, scurvy, beriberi, rickets, Raynaud's disease, leprosy, cervical rib and the *scalenus anticus* syndrome, erythralgia, peripheral neuritis

(One might add lupus erythematosus, periarteritis nodosa, and others—Ed)

Early symptoms of spinal metastatic carcinoma from the prostate are often considered arthritic In Duncan's 85 cases with secondary growths in pelvis and spine, pain was usually worse at night, better when patients got up and walked Spinal motion was freer than in arthritic patients Rosh noted cases of Hodgkin's disease with vertebral involvement

DISEASES OF MUSCLES, AND FIBROUS TISSUE, FIBROSITIS

Fibrositis denotes swelling and proliferation of white fibrous tissue anywhere in the body in response to injury and various toxic influences, with the secondary effect of pressure on arterioles and nerve filaments⁴⁷⁵ It is no more one disease than is arthritis On the basis of supposed cause,

Slocumb noted these etiologic types (1) primary fibrositis—unaccompanied by and independent of, any other definite disease, (2) secondary fibrositis—that secondary to some known cause or primary dominant condition such as trauma, gonorrhea, rheumatic fever, gout, hypertrophic or atrophic arthritis. This groping for order indicates a present knowledge of fibrositis inferior even to that of arthritis. Probably half the symptoms of hypertrophic arthritis are due to associated "senile fibrositis" according to Hunt and Gordon who believe it is due not to foci of infection but to a metabolic fault from impaired circulation and faulty elimination. Treatment of fibrositic nodules, so common with atrophic arthritis, will give some relief (Wilson). The gouty nature of some forms of fibrositis and lumbago was suspected.^{1,1 360}

Primary Fibrositis This condition, of unknown cause and independent appearance is the most common type, "the commonest form of acute or chronic rheumatism" (Scott Slocumb). Almost everyone suffers with one of its forms at least once in his life. Telling called it perhaps the commonest cause of persistent and recurring pain. Copeman and Slocumb noted the two stages of the lesion: the early acute stage of effusion—a mild or severe localized inflammatory (serofibrinous, not cellular) exudate perhaps seen as a puffy swelling, the later stage of organization, with the production of fibrous thickening, nodules and cords.

The anatomic types were listed^{102 49}: (1) intramuscular ("muscular rheumatism," "myositis," "myofascitis"), (2) periarticular (capsular) fibrositis ("capsulitis," "capsular rheumatism"), (3) bursal fibrositis, "bursitis" (4) tendinous fibrositis, for example, palmar or Dupuytren's fibrositis, (5) panniculitis, fibrositis of subcutaneous tissue, (6) perineural fibrositis, "interstitial neuritis," for example some forms of sciatica and brachial neuralgia.

Symptomatology This was reviewed by Slocumb and Copeman. Considering differences in situation of the disease it is obvious why symptoms are so protean. The common characteristic symptoms of the various anatomic types were aching, stiffness and soreness—particularly when the part is put on a stretch, little or no objective changes except the palpable indurations, much fatigue, chilliness and general hypersensitivity. Many cases of indurative headache, lumbago, low back pain and intercostal neuralgia are of fibrositic origin, also many cases of "central or interstitial sciatica."^{3 10-1 0 558} In sciatic fibrositis, pain is referred to the hamstring muscles and not to the nerve trunk which is not even tender until later, reflexes are normal and anesthesia and paresthesia are absent.^{102 150} Albee considers myofascitis the commonest cause of pain low in the back where there are so many fascial insertions into bone and "a more sluggish circulatory condition than elsewhere" (But the blood supply of the back is rich—Ed). Panniculitis, a fibrositis of subcutaneous fibro-areolar fatty tissue, is characterized by disseminated superficial pea-like nodules, so that the skin wrinkles or puckers

when grasped between the hands. The tissue is fatty, tender, and bruises easily. Normal fat is not tender or lumpy. These and other features of panniculitis were described by Telling.

Pathology Data thereon are meager because biopsy is not often made, when made it reveals a vague pathologic picture. Information is available concerning the nodules but not concerning the reaction responsible for such varieties as capsular fibrositis. Sections of nodules from early cases of lumbago show, according to Douthwaite, no recognizable difference from the normal surrounding structures. They give the microscopic appearance of normal excised muscle, since they represent a gel or local coagulum with no cellular infiltration, yet "the nodule is a very real thing." Even chronic lesions reveal no characteristic or striking architectural arrangement, like Aschoff nodules, but are vaguely described as "unhealthy fibrous tissue," "inflamed scar tissue" (Copeman). Certain nodules are not tender, hence some ignore them as of no significance, particularly because experienced persons can feel free nodules in "normal persons." They are not normal but, according to May, always evidence of a previous attack of (sometimes subsymptomatic) fibrositis. Even the nontender ones are potentially troublesome.²⁰⁸ They are often difficult for the inexperienced to palpate. Cases of lumbar myofascitis with palpable nodules are in the minority, according to Albee, who failed to find measurable increases of thickness in affected regions. The more severe cases of fibrositis reveal the most nodules, tender or otherwise. They are usually tender, especially when a nerve twig is implicated, often exquisitely so, when they are pressed the patient squirms and muscles go into spasm. To Douthwaite they do not represent septic emboli, if they did, massage would only aggravate the condition. But for the very reason that firm massage of nodules does often produce slight fever and malaise within 24 hours or so, Scott and Wilson believed they must contain bacteria, probably streptococci and toxins, not toxins alone. Even breaking down old hard nodules is likely to produce reactions. (No data on cultures were given.)

(Most American clinicians have been loath fully to recognize "fibrositis," because its supposed pathology is so ill-defined, its symptomatology so subjective, its chemical reactions "normal." Others who recognize it as a distinctive symptom-complex worthy at least of clinical separation, are nevertheless disturbed by its insecure pathologic basis. Those numerous physicians who, particularly in England, continue to write familiarly of the pathology of fibrositis would immeasurably strengthen their position if, instead of merely briefly restating oft-repeated comments, they would present formal studies with microphotographs showing, as well as possible, the vague reactions which are considered so basic. Until then they cannot escape the suspicion of being guilty of merely repeating what they have read. Many have obviously accepted the work of Stockman (1920) but in the past 20 years of English "fibrositology" few if any have formally attempted to corroborate or advance that work.—Ed.)

Laboratory Data The sedimentation rate is generally normal.⁴⁹⁰ Stuart-Harris found no antifibrinolysins. In stools, Albee found "his-

tamine in large quantities", to him an index of toxicity possibly an etiologic agent

(No quantitative data were given—Ed)

Differentiation Slocumb studied 100 patients with periarticular and intramuscular fibrositis, the commonest forms

About 50 per cent of the patients had both types concurrently or consecutively, 25 per cent each had one or the other type alone. Since many cases of periarticular fibrositis are erroneously called "mild atrophic arthritis" (with its malevolent connotations) differentiation is important. The 100 cases of long chronic fibrositis (total disability 284 years, selection being made to allow maximal local and constitutional changes) were compared to 100 cases of atrophic arthritis, early cases being chosen to see how early the local and constitutional differences would be apparent. Both groups experienced fatigue and nervous exhaustion. Ten pounds or more were lost by 47 per cent of the arthritics, by only 7 per cent of the fibrositics. Roentgenograms were "definitely positive" in 86 per cent of the arthritics (although 50 of them had had their disease less than a year), in none of the fibrositics (except those with occasional incidental senescent hypertrophic arthritis). The sedimentation rate averaged 12 mm (1 hour) in the fibrositics (below 16 mm in 73 per cent, never over 32 mm), 72 mm in the arthritics (normal in only 6 per cent, over 25 mm in 91 per cent, over 50 mm in 67 per cent). Rates were usually elevated within the first six weeks of arthritis. Hemoglobin was below 13 gm in only 5 per cent, below 12 gm in only 1 per cent of the fibrositics, below 13 gm in 42 per cent, below 12 gm in 19 per cent of the arthritics. Occasional patients with periarticular fibrositis exhibited one of these abnormalities, very rarely more. Most of the arthritics exhibited two or more definite, not slight, alterations.

In summary, periarticular fibrositis is readily differentiated from even early atrophic arthritis by the characteristic and persistent negativity of clinical, laboratory or roentgenographic evidence of intra-articular disease or constitutional reaction.

Cases of left-sided thoracic intramuscular fibrositis are occasionally called angina pectoris. Some recognize "mural fibrositis" of the abdominal musculature, often mistaken for intra-abdominal disease. According to Wilson, pain referred to the abdomen results particularly when fibrositic nodules involve the eighth to the eleventh intercostal spaces. Motion of these muscles may or may not cause pain. Differentiation often depends on finding tender intercostal nodules, pressure on which produces immediate referred abdominal pain "or an attack of abdominal pain delayed for some hours or even a day or two."

Etiology The cause of primary fibrositis is unknown. The usual conjectures were entertained: infection²⁷⁶, strain and chill^{3, 69, 102, 106, 151}, "metabolic disturbances"^{69, 150}, "toxicity from intestinal infection or poor elimination³," oxaluria²⁷⁶. Generalized fibrositis is probably an infection, chills and strains produce localized fibrositis^{150, 151, 276}.

(Reading current reports we, with Milliken, were "left a bit vague as to whether myofascitis is due to focal infection, the phases of the moon, or the Hoover administration"—Ed)

Treatment For acute fibrositis the majority favored rest and heat. If the patient is brave, Douthwaite recommended, even in acute cases, vigorous motion of the affected part for 20 minutes, "great, sometimes complete relief is obtained in half an hour." In lieu of active motion, massage was given. English writers again emphasized the "supreme importance and curative value" of their favorite remedy, deep massage "to rub away the nodules." "The only effective cure," it is more useful if preceded by heat (Cruikshank). No other treatment is of such value, the fibrotic change must be treated mechanically, treatment may be painful, tedious and prolonged (Telling). "Break down the fibrous nodule and liberate the imprisoned toxins," to be then eliminated by improved circulation. Specially trained masseurs can do this, although it is painful they must persevere and not be alarmed by the patient's easy bruising (Gordon). Hunt approved the continental axiom: no cure without bleeding. "Massage must therefore be progressively stronger and deeper, and may be energetic enough to cause actual hemorrhages around the nodule." Douthwaite also advocated "deep massage which will probably make the patient yell."

When such massage is too painful preliminary histamine ionization may be useful.^{102, 106} Wilson who of all wrote the most enthusiastically and in greatest detail on the technic and value of manipulative massage to break up the fibrotic nodules, claimed that in some cases it "will in a few minutes relieve pain that has for many years accompanied certain movements of a joint." "Localized tenderness can be made to disappear within a few minutes." Because such massage may "produce a liberation of toxin" and a reaction of fever and malaise within 24 to 48 hours, Wilson and Scott advised that a limited number of nodules be massaged at one session, and massage be given only every three to five days. For old nodules too resistant to be "destroyed" by finger pressure, Wilson described a technic utilizing the sharp but protected blows of a wooden mallet. Manipulation and massage under anesthesia may cure certain cases of chronic lumbago "within five minutes," according to Douthwaite.

(From a limited experience with manipulative massage we cannot match the enthusiasm of our English colleagues, but American clinicians must use this treatment more extensively to criticize it authoritatively—Ed.)

Numerous other measures were recommended. Triple typhoid vaccine, streptococcal vaccine, injections of a local anesthetic or even simple needling of a nodule.^{102, 106} Injections of saline or quinine urea hydrochloride⁵⁴⁸, bee-venom^{57, 397}, histamine by injection or ionization^{57, 102, 106, 157, 306, 481}, colonic lavage^{3, 10-, 106}, dietary and medicinal correction of oxaluria, acidophilus milk, warm climate, low carbohydrate diet, a raw vegetable diet²³⁷. Gold is valueless.^{14, 102, 106} (A refreshing statement—Ed.) Scott noted "a more or less complete disappearance of local disability in 18 out of 25 cases" of intractable fibrositis, usually of 10 or more years' duration, from local injections of a "lipovaccine" (streptococci suspended in olive oil) into nod-

ules A local and general reaction like that from heavy massage was induced within a few hours "Persons who had been in poor condition for years regained their normal color and appearance in a week or two", symptoms abruptly subsided, leaving the fibrositic region comparatively painless

To avoid the common local fibrositis in the neck and shoulders presumably caused by wearing too heavy coats, heavy clothing outside and evening gowns inside the house, with consequent trauma and chilling, Burt recommended warm, but light, clothes, and adequate sweating "Skin-toughening cold showers" may be prophylactic³⁶⁰

Dupuytren's Contracture This starts as a firm, fixed nodule in palmar fascia, usually near the base of the ring finger, affects fascia not tendons, and is generally eventually bilateral Of Meyerding's 273 patients, 45 per cent were physical, 55 per cent mental, workers, 88 per cent were males, age of onset was 17 to 80 (av 54) years Of 273 patients with 448 affected hands, both hands were involved in 64 per cent, the right alone in 25 per cent, the left alone in 11 per cent Fasciotomy is generally inadequate Palmar fasciectomy gave "excellent results" in 89 per cent of 117 hands Postoperative treatment included use of splints, heat, early motion, more active physical therapy after the fourth week^{364, 365}

Epidemic Diaphragmatic Pleurodynia The "devil's grip" is spreading westward in the United States epidemics were noted in late summer and fall of 1934 and 1935 72 cases in Illinois³⁶⁸ and 22 in Colorado,⁴⁰¹ the first two west of the Appalachian Mountains and Mississippi River, 11 cases in Cincinnati⁴⁶ and 282 in southwestern Ohio²⁸⁵ A few patients noted prodromes fatigue, vague abdominal cramps Onset was usually abrupt, with sudden, severe pain in the region of the diaphragm (more often on its thoracic than its abdominal side), lower thoracic wall, often the entire costal margin, also in the epigastrium and upper abdomen Pain shifted from side to side and came in repeated paroxysms (two to nine in all) Sometimes present was pain in back, shoulders, head and neck Other symptoms were fever (100° to 104° F), rapid pulse, leukocytes 3000 to 10,000, no eosinophilia, pallor, nausea, sweating, occasional diarrhea and chill Deep breathing was painful Pain and fever lasted 24 to 36 hours, occasionally three or four days, maximal pain was often between the fourth and twelfth hour The third paroxysm was usually the most painful After three or four days of quiescence a second short attack may appear Friction rub was generally absent (often present in European cases) When abdominal pain is severe, differentiation from "acute abdomen" is difficult, pain may be over McBurney's point but is generally higher and bilateral, the abdomen is fairly relaxed The condition is also mistaken for pleurisy, herpes zoster, coronary thrombosis Recovery was usually rapid and complete Complications were rare (orchitis once)³⁶⁸ Treatment is symptomatic, morphine is required The cause is unknown Small's (1924) plasmodial theory was not confirmed The disease is communicable incubation period being

three to seven days. Blood cultures in six cases were sterile, biopsy of the latissimus dorsi muscle was "negative" ⁵⁶⁷. Age, sex and social status seemed unimportant. Because it occurs in the mosquito season and nearly every one of his patients recalled a recent mosquito bite, Naugle suspected a mosquito-borne disease.

Myositis Ossificans Commonest sites for the traumatic form are the brachialis anticus from injuries about elbow, the quadriceps femoris from "Charley horse," the abductor muscles in horsemen, the deltoids in infantrymen from gun-butt trauma, and the biceps brachii. Hobart noted nine cases. Hamada treated a young girl with myositis ossificans progressiva multiplex.

Calcified Intramuscular Parasites These, presumably cysticercus cellulosae, produced countless discrete, ovoid shadows $\frac{1}{8}$ to $\frac{1}{2}$ inch in size throughout the extremities, abdomen, chest. Muscle biopsy was refused (Lesoff and Schulman).

Trichinosis Asymptomatic trichinous myositis must be very common. At necropsy, McNaught and Anderson found living larvae in 24 per cent of 20 human diaphragms from persons aged 2 to 87 years. The number of larvae was less than 20 per 50 gm of muscle in 79 per cent. No patient had had clinical trichinosis.

Melitensis Infection of Muscle A case of degenerative myositis with temporary muscle atrophy from Malta fever was noted (O'Donoghue and Scott).

Myopathies and Neuromuscular Disorders Further studies on metabolism of creatine and creatinine in myopathies were presented ^{247, 366}, also electromyographic studies in hysterical torticollis, Huntington's chorea, paralysis agitans ³⁴⁶. The use of amino-acetic acid (glycocoll, glycine) was recommended not only for primary myopathies but also to relieve fatigue and creatinuria of muscle disturbances secondary to such conditions as nephritis, scarlet fever, hyperthyroidism, anemia, hyperinsulinism (Terhune and Green).

DISEASES OF BURSAE

The four intermetatarsophalangeal bursae have been ignored in literature. bursitis in one was noted ³⁴³. In Snodgrass' case of compound cystic bursitis of a knee, the suprapatellar bursa and that in the gastrocnemius muscle were connected and both enlarged.

Subdeltoid and Subacromial Bursitis Of the 140 bursae in the body (33 in each upper, 37 in each lower extremity) the subdeltoid is most often diseased (Echtman). Of 300 consecutive painful shoulders studied by Haggart and Allen 80 per cent were caused by subacromial bursitis, 6 per cent by arthritis, 8 per cent by myofibrositis, 6 per cent otherwise. In Lee's cases, trauma seemed to be a factor in 50 per cent, the right shoulder was affected twice as often as the left, 75 per cent of patients were males. Many cases of Weeks and Delprat were preceded by upper respiratory infections. Current ideas on etiology, differential diagnosis and therapy were reviewed.

Echtman first applied cold applications, then heat, massage and manipulation, diathermy for cases with calcification, for stubborn cases galvanization or ionization with magnesium sulphate. Lee used immobilization in abduction and external rotation, surgical removal of chronic painful calcium deposits. Lattman stated that roentgen therapy relieves pain and restores function faster than anything else; good results were noted in 15 of 20 cases, one or two treatments reputedly relieved pain in 24 to 48 hours. Rapid relief may follow simple aspiration of bursal fluid, even the mere procedure of needling (multiple punctures at one session) is often helpful whether calcium deposits are present or not (Weeks and Delprat). Haggart and Allen advised for acute bursitis exploration and drainage of the calcified material or procaine injection, for chronic bursitis, physiotherapy, exercises (diagrammed), occasionally procaine injections, for chronic adhesive bursitis, drainage of calcified material, manipulation to loosen adhesions, or procaine injections, physical therapy, exercises. The latter cases without calcification may need elevation and traction in a Balkan frame.

(Calcium deposits often rapidly disappear spontaneously. Their surgical removal should be advised with caution—Ed.)

OTHER STUDIES

Articular Roentgenography The "articular space" as referred to by roentgenologists is a misnomer, it is not the true space but translucent interosseous material, cartilage and ligaments. With improved technic, Widmann and Stecker visualized the true articular space in normal knees and shoulders, not elsewhere. Friedman described an improved roentgenography to show hip joints laterally.

Arthroscopy Further observations on the technic and value of arthroscopy and punch biopsy were reported (Burman, Mayer and Finkelstein). The procedure was technically successful and caused little or no articular reaction, but diagnoses on specimens obtained at biopsy did not always conform to those later made at surgical operation.

Articular Function A method for measuring and recording joint function was described (Cave and Roberts). Jones applied engineering principles to the study of human joint lubrication and determined coefficients of friction of interphalangeal joints. The usual form of lubrication of human joints is by a fluid film which survives a load which can crush bone.

Articular Physiology The metabolic requirements of articular tissues must be known before one can properly discuss the problem of articular nutrition. Bywaters studied the metabolism of normal and abnormal cartilage and synovia.

Cartilage possesses slight but definite glycolysis which, per cell, is similar to that of rabbit liver or kidney. The CO₂ present all comes from lactic acid. Glycolysis was inhibited by fluoride, increased by phosphate. Oxygen consumption of cartilage was small but greatly increased by methylene blue. The metabolism of synovial

membrane is about the same as that of other adult tissue. Transformations affected by synovia seemed similar to those of ordinary connective tissue except for its very low respiratory quotient for which there is no comparable figure. Inflamed villi have an increased metabolism out of proportion to cell increases. The metabolism of cartilage and synovia is similar in humans and horses. The cartilage metabolism of a horse with degenerative arthritis, and of a woman with atrophic arthritis was normal. Synovial fluid contains twice the amounts of glucose necessary for cartilage.

(For a better understanding of articular diseases many such studies are necessary—Ed.)

The growth mechanism of articular cartilage as seen in animals of various ages, involves cell division, mitotic in the young, amitotic in older ones. Elliott regarded amitosis an active process of tissue proliferation, not the result of mechanical insults, degeneration or mere necessity of increasing nuclear surface.

Further studies were made on the rôle of the reticulo-endothelial system in the deposition of colloidal and particulate matter in articular cavities (Kuhns and Weatherford). Colloidal and particulate matter is carried by blood to joints from various body tissues, skin, the gastrointestinal tract. It is stored chiefly in histiocytes in synovia, also in bone marrow, lesser amounts in intermuscular septa and articular fat pads. Mild inflammation in joints increases the deposition of such transported substances. Local blocking of the reticulo-endothelial system is transitory, incomplete, and ineffective in preventing deposition of colloidal and particulate matter in joint tissues.

Muscle Physiology Studies on electrolyte changes in muscles during activity¹⁷¹ and on the circulation in striated and plain muscles in relation to activity⁶ were reported.

Physiology of Tendons Cronkite studied the tensile strength of 294 human tendons from cadavers and autopsy material. Certain errors of technic were inherent in methods used. Tensile strength ranged from 8700 to 18,000 pounds per square inch of surface. Right- and left-sided tendons did not vary in strength, nor did flexor or extensor tendons of hands. No one tendon in the body was consistently strongest. There was no correlation between tensile strength and age or cause of death. A historical note on the origin of the term "tendo Achilles" appeared (Couch).

Additional Of interest also were studies by Steindler on physical properties of bone, by Biernan on skin temperature as affected by various physical and chemical factors: age, fever, disease, heat, cold, anesthesia, drugs, tobacco, whiskey, humidity, air motion.

CAMPAIGN AGAINST RHEUMATIC DISEASES

The caliber of much of the work reported herein permits one to agree with Weil that rheumatology is no longer "that cloaca of ignorance" so scornfully referred to by Haygarth. The brightest side of rheumatism is the growing interest physicians are taking in it. They realize the necessity

of meeting its challenge instead of sidestepping it.¹⁸⁸ Often the family physician, working with consultants and social agencies, will find at hand adequate facilities for managing his arthritic patients. But the army of arthritic and cardiac cripples attests the inadequacy of our attack. Although in the United States there are more cases of chronic arthritis and "rheumatism" than of cancer, tuberculosis and heart disease combined and although almost every state and county has a special institution or other facilities for treating tuberculosis, not a single county or state in the United States has a special institution for the care of arthritics except Boston which has the Robert Brigham Hospital.

(However, many hospitals and clinics have departments for the special study and care of arthritics—Ed.)

From a survey of 89 hospitals, Kling concluded that none of the institutions, city or county, general, church, university or even orthopedic hospitals, are extending adequate facilities to arthritic victims. All gave very low admission rates for arthritics (0.85 to 2.3 per cent). There are about 646,000 tuberculous patients in the country of which 363,000 are bedridden. To the 87,000 beds available for them, about 156,000 tuberculous patients are admitted annually. In other words, one of every four sick or one of every two bedridden tuberculous patients is provided with institutional care, generally for the duration of active disease. In contrast, hospital facilities were available for less than 10 per cent (98,000) of our 1,020,000 bedridden rheumatic patients. About 90 per cent of beds for the tuberculous are free, very few free beds are available for arthritics. Physicians in charge of tuberculosis devote themselves largely to this disease, but most rheumatic patients are cared for by "physicians with little interest and very inadequate facilities." There is therefore great need for state sanatoria or community funds for hospitals and teaching centers to care for and rehabilitate those persons unable to attend spas and health resorts, and to allow study of all aspects of these diseases.^{181, 269, 3-9} But to avoid a narrow viewpoint, rheumatism centers should be established in connection with general hospitals and general clinics, not as segregated institutions for arthritis (Irons).

In England also the few existing facilities merely touch the fringe of the problem, which must be attacked as was that of tuberculosis. England must have a changed outlook, and realize that rheumatism although chronic, is an acute problem (Elman). In that country the disease is largely unchallenged. The Red Cross Society Clinic in London is "the only one in England solely devoted to treating rheumatic diseases." Copeman reviewed its activities. 80,000 to 90,000 patients (visits or registrations?) are seen yearly. "Every city and industrial center in England should be a candidate for such a clinic." Other angles of the campaign were outlined in Horder's report of the activities of the British National Society for the Control of Arthritis, and in Van Breemen's report of the organization, function and aims of the International League against Rheumatism.

Denmark and Sweden are courageously facing the problem Kahlmeter regarded the value of Sweden's specialized hospitals self evident Various other methods were adapted to bring rheumatic diseases under control institutions for research and for the training of rheumatism specialists, consultation clinics for rheumatic patients allied to hospitals and physical therapy units, proper development of spas, utilization of social service departments

Noting the meager instruction on joint diseases given to medical students, Johnson believed instruction should be the duty of clinicians But clinicians already have too large a share of the curriculum and have inadequate hospital material to present because hospitals are so niggardly in the admission of arthritic patients Orthopedists, with their abundant (if late) material, should therefore accept the duty and welcome the opportunity to "become physicians again" The rheumatic problem should be taught in four ways by lectures, ward classes, dispensary services, and in the libraries and laboratories It should be taught, not dogmatically, that is not safe, not by an advocate of any one theory, one may be pleading a bad cause, not by an experimenter, that is too complex for the student It should be taught by the philosopher with a broad dispassionate viewpoint, by one who above all else avoids the semblance of authority

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AN ARTICLE CONTRIBUTED TO AN ANNIVERSARY VOLUME IN HONOR
OF DOCTOR JOSEPH HERSEY PRATT

A RARE MANIFESTATION OF GOUT, WIDESPREAD ANKYLOSIS SIMULATING RHEUMATOID ARTHRITIS *

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ANKYLOSIS may occur in gout. Such ankylosis results because of monosodium urate deposits in the articular tissues. The presence or absence of ankylosis in gout is dependent upon the extent of the urate deposition, its location and the reaction of tissues involved. Ankylosis in gout, however, is rare. When it does occur, it is usually limited to one or two joints, most commonly the small joints of an individual 40 or more years of age, who has been the victim of gout for a long period of years^{1, 2, 3, 4}. Most of the references concerning ankylosis in gout are to be found in the writings of the latter half of the last century. All too frequently, it is merely mentioned without describing the pathological changes encountered.⁵ Others^{6, 7, 8, 9, 10, 11, 12, 13, 14} have described in detail the articular changes resulting from gout. Virchow, as early as 1868, reported a case with complete ankylosis of the terminal phalangeal joint⁶ of the great toe. Rarely is widespread ankylosis mentioned, although Litten¹⁵ reported such a case in 1876.

The present case is sufficiently rare to justify a published account because of (1) The relative youth of the patient, (2) the severity of the gout, (3) the rapidity with which extensive intra-articular changes resulting in widespread ankylosing deformities occurred, and (4) the clinical picture presented by the patient, which when first seen so closely simulated that of an individual with extensive rheumatoid arthritis.

CASE REPORT

F N, a white, single, native-born salesman, aged 28 years, was admitted to the medical wards of the Massachusetts General Hospital on December 17, 1934.

Family History There was no known occurrence of gout or arthritis in the patient's relatives. His father, a very obese man, died of a cerebral hemorrhage at the age of 50.

Past History The patient had never been ill except for attacks of measles, chicken pox, mumps and influenza, all without any complications. He had injured the arch of his left foot playing foot-ball some years before the onset of the present illness. This resulted in chipping of one of the small bones of the foot. The bone

* Received for publication August 16, 1937.

This is publication No. 23 of the Robert W. Lovett Memorial for the study of crippling disease, Harvard Medical School.

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chips were removed in 1925. He had been an individual of extremely good habits and had always been fond of athletics prior to the onset of his present illness. He used neither alcohol nor tobacco.

Dietary History His diet had always been very adequate and well balanced in every regard. His consumption of meat had been normal. He habitually ate liver once a week, but did not ordinarily indulge in foods of high purine content such as brains, kidneys, or sweet-breads. He did not use chocolate or cocoa.

Present Illness In February 1927, at the age of 21, he had his first attack of arthritis. The onset was sudden, without preceding infection or other prodromata such as one frequently observes in rheumatic fever, rheumatoid arthritis, or gonorrheal arthritis. He first noticed severe pain in the left ankle with marked swelling and redness. It was exquisitely tender. There was an associated fever. The right ankle, both knees and both hips were subsequently similarly affected. The arthritis was migratory in nature, tending to clear in one joint (but never completely) before another joint became involved. With subsidence of the swelling, desquamation of the skin overlying the joint occurred. The total duration of the attack was four to five weeks, following which all joint signs and symptoms gradually disappeared. He made a complete recovery without any residua. He had received only symptomatic treatment. A tonsillectomy was done in April 1927, as a preventive against future attacks. Shortly afterward, he was accepted for life insurance.

He remained absolutely symptom-free and apparently well until March 1928, when he suffered another attack of acute arthritis, almost an exact duplicate of that of the year before in that it was of sudden onset, polyarticular and migratory in nature, with associated fever. The same joints were involved. This attack lasted four to five weeks and was again followed by complete recovery. Recovery from this self-limited attack was credited erroneously to the use of several intravenous injections of orthodoxy-benzoic acid.

In 1929, he experienced a similar attack of arthritis again followed by a year of complete freedom. He suffered from a recurrence in 1930 during which he had involvement of the shoulders, elbows, wrists, and fingers for the first time. Injections of "serum" were given without benefit. This attack lasted about the same length of time. He again made a complete recovery, but had two similar attacks of arthritis that same year.

During the next two years, he had two or more such attacks. In 1932, he had dysuria on one occasion following which he passed a small amount of gravel (probably small urate stones). This same year, he noted increasing stiffness of the ankles. Since then, he has had to use a cane or crutches for walking. In 1933, his right wrist and several fingers became stiff. During the 12 months prior to admission he had four attacks of arthritis. These had occurred in November 1933, March 1934, September 1934, and November 1934. The last of these attacks which began three weeks prior to entry caused him to seek further medical aid. The onset had been sudden and was marked by swelling, redness and pain of the ankles, wrists, knees, hips, shoulders, elbows, wrists and fingers. Following each of these last-mentioned episodes, there was increasing stiffness and deformity of the joints involved. The temporomandibular and vertebral joints had never been involved.

The patient had been on a high vitamin-low carbohydrate diet since 1931. This was without effect on the joint symptoms but did result in a 45-pound weight-loss.

COMMENTS ON HISTORY

This case history is of importance in that it illustrates many diagnostic points characteristic of the gouty patient and his arthritis as well as some of the unusual features of this particular case.

In attempting to make a correct diagnosis in the case of patients suffering from joint disease, an accurate history is most important. A detailed history will enable one to suspect the correct diagnosis in the majority of the cases. In the remaining few, a complete physical examination and one or two well chosen diagnostic laboratory tests are needed. In an occasional patient, a biopsy may be necessary and most helpful. In rare instances, the passage of time and further observations are indispensable.

In recent years, Hench^{16, 17, 18} has tried to make the physicians of this country gout-conscious. In attempting to do so, he has repeatedly stressed as have others^{19, 20, 21, 22, 23, 24, 25} in the past the importance of an accurate history. In many instances it alone is sufficient to make a "presumptive" diagnosis.¹⁶ Certainly a suspicious history should always call for a therapeutic test with colchicin. If marked or complete relief always ensues 24 to 72 hours after the onset of colchicin toxicity symptoms, the diagnosis is for practical purposes established. This therapeutic diagnostic test can and should always be carried out even if uric acid determinations are not possible.

In this particular case, the history of recurrent attacks of arthritis, with absolutely complete freedom from joint symptoms between each attack for a period of five years before any permanent joint changes took place, is of itself highly suggestive that the patient had suffered from recurrent gouty arthritis which had finally become chronic.

Recurrent polyarticular, migratory arthritis with associated fever in a young adult would naturally suggest the possibility of recurrent or cyclic rheumatic fever. In this case, however, there were no preceding upper respiratory infections nor any of the other precipitating factors occurring some 7 to 14 days prior to the onset of each attack of arthritis which are so frequently observed in rheumatic fever. None of the associated symptoms of rheumatic fever such as weight loss, skin eruptions, nodules, nose bleeds, tachycardia, precordial pain, etc., was present. Furthermore, with migration of the arthritis, the previously affected joints did not clear so promptly as they regularly do in rheumatic fever. There were no symptoms suggestive of heart disease such as one might rightly expect in a patient who had had so many recurrent attacks of rheumatic fever.

Polyarticular involvement occurs in about 5 per cent of all cases of gout.¹⁶ The younger the individual, the more likely it is to be polyarticular. The polyarticular involvement may be simultaneous or of the migratory type. This form of gout rarely involves the large toe and the attacks are of long duration, usually weeks instead of 7 to 10 days. The fever is more marked and may last weeks. This type is rarely afebrile.²⁵ It signifies severe gout. It is frequently misdiagnosed rheumatic fever.

A specific infectious arthritis due to the gonococcus is sometimes characterized by recurrences. We have seen one individual who experienced eight such recurrent attacks of arthritis due to a latent focus. In such instances, the story is quite characteristic. There is usually an exacerbation or

recurrence of the genito-urinary symptoms. Particularly is this true in the male. On the same day or a few days later, the patient experiences a chill or chilly sensation followed by fever and migratory aches and pains or a migratory arthritis. This usually subsides after a day or two, leaving one or two joints involved which may show mild or severe inflammatory signs with a corresponding amount of joint pain, etc. Rarely does it remain polyarticular. Although the swelling and other signs of inflammation may be quite severe, they are rarely of the same severity as those seen in gout, where the swelling is more marked, extending further beyond the joint margins than in any other type of arthritis, with the possible exception of certain cases of septic arthritis. Acute gouty arthritis more nearly resembles septic inflammation or extensive cellulitis. There may be an associated lymphangitis. In gouty arthritis, the pain is severe, often described as crushing, worse during the night, letting up in the early morning. The patient protects the joint in every way possible. The overlying skin is red, tense and shiny. The superficial veins are markedly distended. The tenderness is exquisite. As the tenderness subsides, pitting edema is demonstrable. With disappearance of the joint swelling, desquamation of the cuticle and itching follow.

Rheumatoid arthritis in 18 per cent of the cases is characterized by an atypical onset and in 7 per cent may remain atypical for some time, hence the more appropriate name atypical rheumatoid arthritis³². This is the group which is all too frequently labelled focal infectious, toxic or non-specific infectious arthritis. The first attack is often acute in onset in an individual who had previously considered himself well. These patients are usually robust and not the asthenic type of individual with evidence of increased vasomotor activity, etc. The attack may or may not be associated with an acute infection or an obvious focus of infection. The joint involvement is usually asymmetrical. It may be polyarticular and migratory. The monoarticular form is encountered. Recovery from the first attack may be complete and if so is often ascribed to some therapeutic procedure whereas it truly represents the first self-limited attack of an acute, atypical rheumatoid arthritis followed by apparent recovery. The remission following such an attack is variable. It may be of only a few months' duration, occasionally a year. However, in most instances, it will eventually be followed by a relapse. An individual may have a number of such recurrences and remissions before the disease becomes chronic. As a rule, the remissions are not complete. Frequently there remains certain tell-tale evidence of the previous joint involvement. Rarely if ever will one encounter a case of rheumatoid arthritis with a history similar to that of the patient herein described, of 12 or more acute attacks of arthritis each followed by absolute and complete recovery without residual joint deformity. The marked joint signs, subsequent desquamation, itching, etc., seen in this case are not encountered in atypical rheumatoid arthritis. At

the stage of atypical rheumatoid arthritis where many joints are deformed one will usually find that the joint involvement, particularly of the small joints, is symmetrical.

The typical case of rheumatoid arthritis with preceding constitutional, vasomotor and neurological symptoms, insidious in onset, characterized by symmetrical joint involvement (usually the small joints), should rarely if ever be mistaken for any type of gouty arthritis. In cases with chronic joint deformity with ankylosis due to gout, tophi and other evidence of the disease will be present.

The eliciting of a history of renal colic with the passage of a stone or gravel in an individual suffering from recurrent arthritis should always lead one to suspect gout as the cause of both symptoms.

This patient is of further interest because of the early age (21 years) at the time of onset of his gouty arthritis. The average age of onset has been recorded as 40 years^{16, 25}. Pratt states that the youngest case he saw with tophi was a man of 28 years²⁵. He further states the disease seldom develops before 20 years of age. One patient observed in this clinic may have had his first attack at nine years of age (it was diagnosed tuberculosis of the hip at that time and he was treated with plaster casts). From the ages of 14 to 19 he had numerous recurring attacks of polyarticular migratory arthritis accompanied by fever. They were always followed by complete recovery. They had always been diagnosed rheumatic fever although he had no endocarditis. When first seen at 19 years, he had a whole blood²⁶ hyperuricemia of 9.2 mg per cent. It has continued to run between 12.3 and 14.8 mg per 100 c.c. serum^{26, 29, 30}. He has since developed tophi (age 20 years). Undoubtedly such cases of gout are frequently mislabeled rheumatic fever because of the youth of the patient and the close similarity to rheumatic fever. Such mistaken diagnoses can be avoided if we will become gout-conscious. Repeated careful questioning at each visit will often result in the patient being able to recall earlier attacks which he had failed to mention at the time of his first visit. Such attacks frequently follow slight athletic injury, and are diagnosed sprain or strain, although the severity and duration of symptoms are consistent with a monarticular form of gouty arthritis.

In this instance, there was no family history of gout. There can be little doubt that the frequency with which data indicating heredity are obtained depends upon the degree of thoroughness of the inquiry. Again oft-repeated questioning on subsequent visits plus repeated questioning by the patient of his relatives will result in positive information which had been denied previously.

This patient knew of no precipitating factors. He did not consume excessive quantities of high purine foods and his attacks did not follow gastronomic sprees. We were unable to elicit evidence of attacks following major or minor physical trauma, such as fractures, dislocation, injury

wearing of tight shoes, after unusual use of a joint, etc,¹⁷ nor did they follow "physiologic trauma" resulting from protein therapy, severe purging, loss of blood, exposure to cold and wet, etc.¹⁷ He thought worry might have contributed.¹⁷ Such precipitating factors should always be sought. In this case neither of the patient's operations induced an attack.¹⁷ Hench has repeatedly stated "*suspect gout in cases of acute postoperative arthritis particularly in males*"¹⁷ This warning is well worth remembering. Operative procedures may also induce an exacerbation of rheumatic fever. In such instances there is the usual latent period of seven to 14 days between the operation and the onset of the arthritis. Although rheumatoid arthritis is frequently followed by immediate improvement, usually shortlived, following surgical procedures, it is occasionally activated or increased in severity. This is probably an effect of the ether anesthesia and not due to the removal of an obvious focus of infection.

The prodromata preceding an attack of gouty arthritis are variable. Some state that they feel their best before each attack, others complain of nausea, indigestion, melancholia, polyuria, nocturia, stiffness, aching, etc.

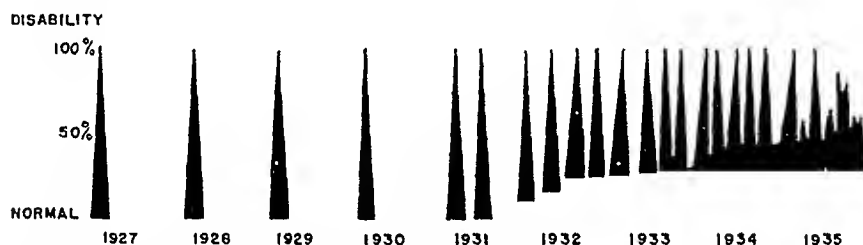


FIG 1 This schematic chart depicts the frequency of the recurrent attacks of acute disabling gouty arthritis experienced by this patient. It will be noted that one such attack occurred each spring for the first four years. They then increased in frequency. Residual joint changes were present after the first five years. (Each peak represents an attack. The solid black area from 1932 on indicates the approximate disability present.)

From figure 1 it will be noted that the attacks first came once a year, usually in March or April. More attacks occur between April and June than at any other time of the year.¹⁷ After four years, the frequency of attacks increased to two to four per year and at the end of five years, the patient had residual joint deformity. The time between the first and second attacks is variable. It may be months or years. In 100 cases, the patients averaged one attack every 1.7 years.¹⁶ The average for each attack was 13 days. The interval between attacks becomes less with each subsequent attack until chronic joint deformity becomes evident. To have as marked crippling at the end of five years as was noted in this case is most unusual. Such marked crippling is more apt to be seen in the polyarticular form and represents the more severe type of gout. Only 2 per cent of cases of gout are chronic from the onset.¹⁶

An important thing to remember is that gouty patients feel unusually well between their attacks, as one patient stated, "my arthritis is almost

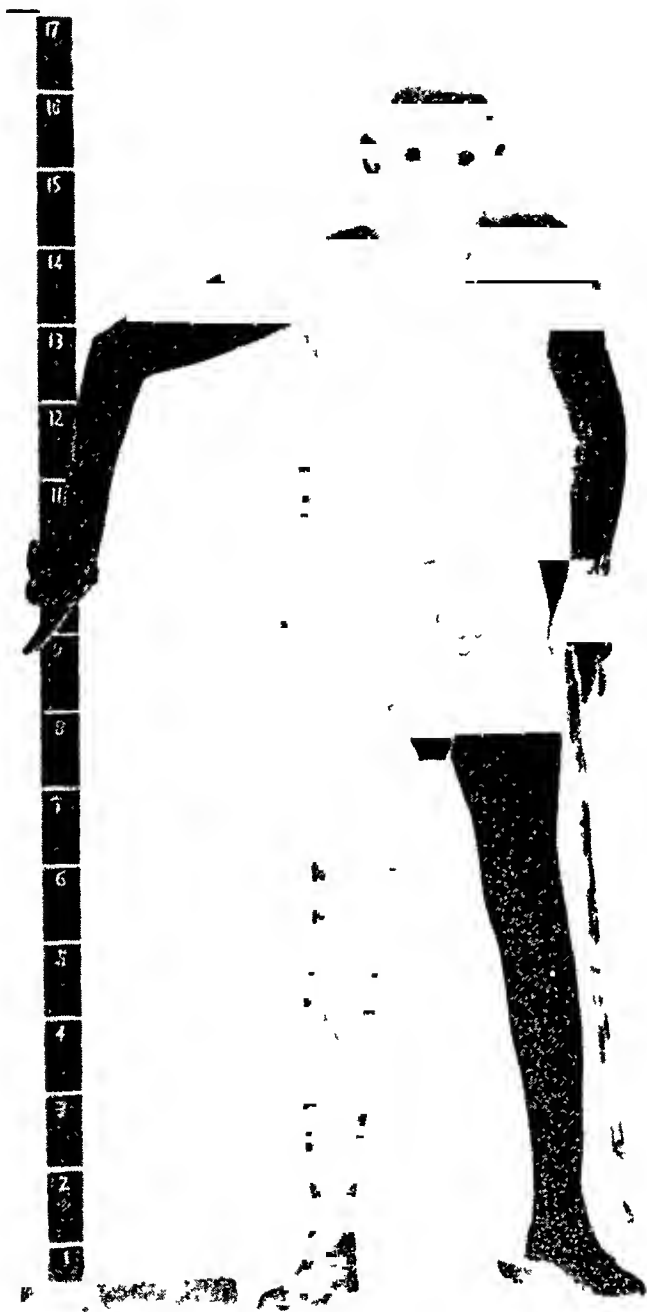


FIG 2 This anterior view of the patient shows the degree of disability present at the time of entry. He had to support himself because of the flexion contractures of the knees and the ankylosed ankles. The equinus deformity of the left foot is apparent. The manner in which he grasped the measuring stick and cane serves to illustrate the deformities of the elbows, wrists and fingers.

unbearable, yet between attacks, I am as fit as a fiddle" The attacks of arthritis are self-limited Many of the so-called specific therapeutic measures for rheumatoid arthritis such as vaccines, sera, colloidal injections, removal of infected foci, colonic irrigations, endocrine therapy, etc., are prescribed and erroneously given credit for curing an attack of rheumatoid arthritis, whereas the patient was suffering from a self-limited attack of gouty arthritis

PHYSICAL EXAMINATION

The patient was examined on December 17, 1934 He was a fairly well developed, moderately obese young man (figure 2) The skin of the hands was cool and moist There were erythematous patches on the skin of the cheeks and forehead, with scaling of the forehead Brownish pigmentation of the skin was present over the dorsum of the hands and feet, the fingers, and the toes Over the interphalangeal joints of the fingers, the skin was dry and scaling The eyes, ears, nose, throat and sinuses were not remarkable The tonsils were out The teeth and gums were in good condition The lungs were normal to percussion and auscultation The heart was normal in size, the sounds of good quality, the rhythm regular, and there were no murmurs The systolic blood pressure was 124 millimeters of mercury, diastolic 90 Examination of the abdomen revealed no abnormality The knee joints were difficult to obtain, other reflexes could not be tested because of the extensive joint involvement The prostate was normal Prostatic massage yielded no secretions

There was a lesion resembling a tophus on the left ear Nodular enlargement of the left olecranon bursa was present There was a suggestion of beginning subcutaneous tophi over the terminal phalangeal joint of the right index finger (figure 3A)



Examination of the Joints All the finger joints were affected. There was a slight flexion deformity of the terminal phalanges of the second, third, fourth and fifth fingers of both hands. The interphalangeal joints of the right second, third and fourth fingers were ankylosed in a position of 10° hyperextension. The left second, third and fourth fingers were similarly involved (figure 3A). There was slight flexion of the left fifth interphalangeal joint. Ankylosis, with slight flexion deformity, and subluxation of the interphalangeal joint of the left thumb were noted



Fig 3 B



Fig 3 C

There was tenderness and limitation of motion of the metacarpophalangeal joints on both sides, more marked on the left. The grip of the right hand was poor, and there was inability to flex the fingers. The grip of the left hand was fair. The skin over the finger tips was atrophic. There was marked atrophy of the interosseous muscles of both hands. Lateral pressure applied to the palms proved to be painful on both sides. The right wrist was completely ankylosed in 35° of flexion. The elbows could be fully flexed, but they lacked 10 to 15° of extension. There was no limitation of motion in the shoulders, although pain resulted with extremes of motion. The dorsal and lumbar spine showed very slight limitation of motion in all directions. The cervical spine was normal. The sacro-iliac joints were normal. The temporomandibular and sternoclavicular joints were uninvolved. There was about 40 per cent limitation of motion in all directions in both hips. The right knee was limited in motion. It lacked 30° of full extension. Flexion was possible to an angle of 60° . The left knee lacked 15° of full extension, and could be flexed only to about 60° . The quadriceps pouch insertion was thickened on both sides. Grating was palpable on motion of both knees. The patellae were not movable. Synovial thickening and irregularities of the articular margins of the knees could be detected on palpation. The left ankle was nearly completely fused in 10° of extension, only a jog of motion

being present in any direction. Motions of the right ankle were markedly limited. Both feet were almost completely fixed. Lateral pressure applied to the metatarsophalangeal joints was painful. Only slight flexion or extension of the toes was possible. All of the toes deviated laterally.

COMMENTS ON PHYSICAL EXAMINATION

The admission diagnosis was chronic infectious or rheumatoid arthritis. The diagnosis of rheumatoid arthritis after complete physical examination seemed justified because the patient exhibited many of the features commonly encountered in this disease, increased vasomotor activity, brownish pigmentation of the skin of the hands and feet, widespread joint involvement with extreme ankylosis (figure 2), the characteristic appearance of the hands and fingers (figure 3A) (shiny atrophic skin with hyperextension and flexion type of deformities of the fingers) and supposed rheumatic nodules in the olecranon bursa (figure 4). However, subsequent examinations revealed a suggestive tophus in the left ear (figure 5). Dissolving



FIG 4 Photograph of the left olecranon bursa. It contained numerous, hard, nodular tophi.

the material obtained from this lesion with hydrochloric acid revealed uric acid crystals. The material gave a positive murexide test. This finding led to the suspicion that the olecranon bursa and the swelling over the terminal phalangeal joint were also tophi. Subsequent examination of material obtained from them confirmed this suspicion.

If one suspects gout, he should make a diligent search for tophi. Subcutaneous tophi are most commonly found in the helix of the ear. They are white, cream-colored, or yellow, varying in size from that of a pin head to a pea. Except in severe gout they rarely appear before 10 years¹⁶



FIG 5 Tophus seen in the right ear

They are pathognomonic of gout but should never be considered such until the monosodium urate crystals have been demonstrated or until a positive murexid test is obtained. They are also found in the cartilage of the nose, along the tendons of fingers, hands, toes and feet and the patellar tendons, patellar and olecranon bursae. The last-mentioned should not be confused with the bursal and subcutaneous nodules of rheumatoid arthritis (figure 6) or rheumatic fever. When the skin overlying a tophus breaks down, a mixture of chalk and water is discharged. The old discharging tophi contain hard chalk-like material.

Although gout commonly affects the big toe, it does so in only 54 per cent of the cases in the initial attack¹⁶ As can be seen from this case, almost any joint may be involved. This is true whether the arthritis is mono- or polyarticular. Evidently the spine and sacro-iliac joints are rarely involved. Joint effusions do occur. The temporomandibular and sternoclavicular joints, relatively frequently involved in rheumatoid arthritis, are rarely affected in gout.

If the initial examiner had been gout-minded, he would not have overlooked the ear tophus and would have correctly interpreted the olecranon bursitis.

INTERPRETATION OF ROENTGENOGRAMS

December 1934 Roentgenological examination showed extensive changes in most of the joints examined. The joint spaces of the middle phalangeal joints of all the fingers were narrowed. Irregularity of the articular surfaces was present in the

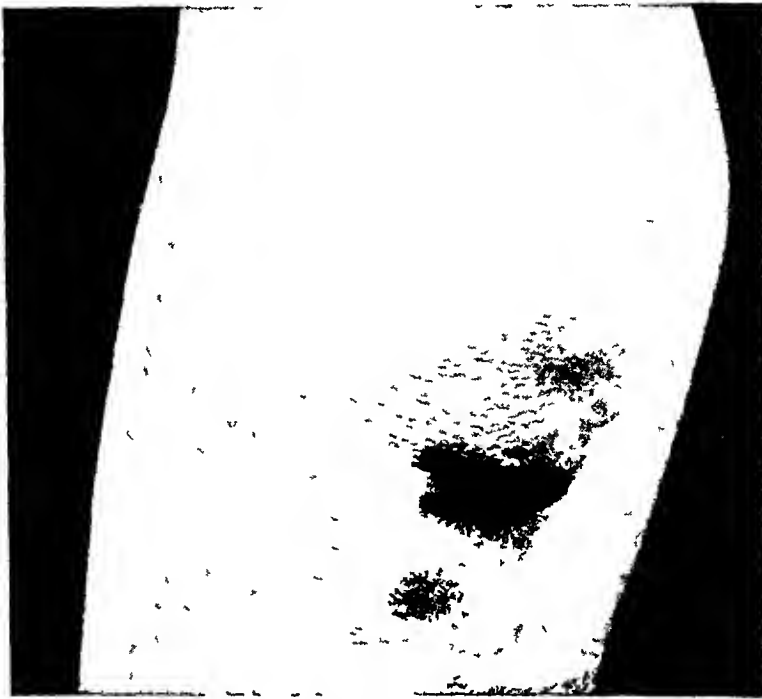


FIG 6 Rheumatic nodules in the olecranon bursa of an individual suffering from rheumatoid arthritis. The nodules had been present for one year.

middle phalangeal joints of the little fingers, the left being fused (figure 7). Similar changes were seen in some of the terminal phalangeal joints of both hands (figure 7). There was gross destruction and deformity with partial dislocation of the first and second left metacarpophalangeal joints. The right wrist showed irregularity of the joint surfaces with narrowing of the joint spaces. The changes in the left wrist were slight. There was narrowing of the joint space of the elbows. The film of the pelvis showed irregularity and indistinctness of the outline of the left sacro-iliac joint. There were marked hypertrophic changes about the right knee (figure 8). An anteroposterior view of the left knee showed narrowing of the joint space (figure 8) (due in part to the flexion deformity). There were small irregular areas of decreased density in the central portion of the articular surfaces of the femur and the corresponding area of the tibia. The feet and ankles showed changes similar to those seen in the wrist and finger joints (figures 9 and 10). There was calcification of pelvic and leg vessels.

Diagnosis All of these changes were thought to be consistent with infectious arthritis. The hypertrophic changes in the knees were interpreted as being secondary to a previous infectious arthritis.

March 1936, 16 months later At this time the joint changes mentioned above were found to be more extensive. The narrowing of the joint spaces had increased. There was more new bone formation and the deformity of joint surfaces was more

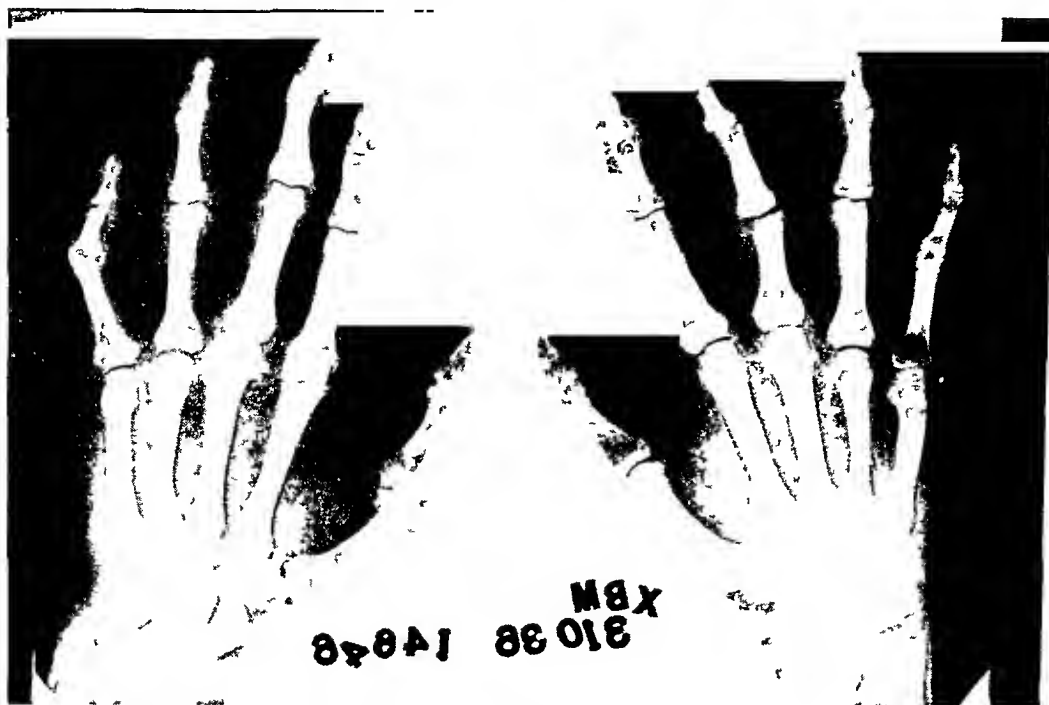


FIG 7 Roentgenograms of the hands, showing decalcification of the bones of the fingers in the region of the joints. Narrowing of many of the phalangeal joint spaces is present. Similar changes are present in the terminal phalangeal joints. Irregularity of the articular surfaces of the middle phalangeal joints of the little fingers is seen, the left being fused. The punched-out area in the distal end of the phalanx of the right second finger appeared in one year's time. There is marked destruction of the metacarpophalangeal joints of the first and second left fingers. The distal end of the phalanx of the right third finger is amputated. The right wrist shows irregularity of the joint surfaces and narrowing of the joint spaces.



FIG 8 Anteroposterior and lateral views of the right knee, showing some decalcification of the bones, narrowing of the joint space and marked marginal overgrowth of the femur and tibia.

marked. The distal extremity of the right third finger had been amputated (surgical) (figure 7). There was partial fusion of some of the tarsal joints. There was obvious destruction and deformity of both the first as well as the second left metatarsophalangeal joints. Localized punched-out areas were present in the bones of



FIG 9 Anteroposterior roentgenogram of the feet demonstrating decalcification of the ends of the phalanges and joint narrowing. Areas of destruction and punched-out areas are present in the bones of both the first metatarsophalangeal joints.

the distal extremity of the middle phalanx of the right index finger, and adjacent to both first metatarsophalangeal joints (figures 7 and 9), as well as at the superior margins of the left os calcis. There were similar but less marked areas of destruction in the metacarpophalangeal joints of the left first and second fingers, the right fifth finger, and the proximal phalangeal joint of the fifth finger. Bone atrophy was present to a marked degree in the bones of the ankles, moderate in the hands and feet. There was some soft tissue thickening about the joints showing bone destruction. The disease was symmetrical in character, several of the phalangeal, metacarpophalangeal and metatarsophalangeal joints being normal. There was calcification of the blood vessels in the lower extremities.

Roentgen-ray examination of the teeth showed unerupted upper third molars, and several malposed teeth. Roentgen-ray study of the sinuses, lungs, heart, abdomen, colon, kidneys and gall-bladder revealed no abnormalities.

COMMENT ON ROENTGEN-RAY INTERPRETATION

The roentgen-ray findings suggestive of gout are punched-out areas, usually 5 mm or greater in diameter, most commonly located in the subchondral bone of the base or head of the phalanges of the hands and feet. Such changes may be late in appearing. In Hench's series,¹⁶ 19 cases with tophi and hyperuricemia had had their disease 28 years or longer and yet

no roentgenographic changes were present. Marginal hypertrophy of the bones involved is a frequent finding. These subchondral punched-out areas are not to be confused with those seen in hypertrophic arthritis and rheu-



FIG 10 Lateral view of the left foot showing the marked decalcification, destruction of joint surfaces, and ankyloses

matoid arthritis. In the latter, generalized decalcification is usually present. Occasionally similar findings are encountered in the case of the gummata of syphilis, leprosy and yaws as well as in tuberculosis and sarcoid.

In this case the roentgen-ray findings were most misleading because of the widespread involvement, marked destruction and deformity, decalcification of the bones of the involved joints and obvious ankylosis. These changes resemble more nearly those of a specific infectious arthritis or rheumatoid arthritis. Marked hypertrophic changes at so early an age are most commonly secondary to a preexisting rheumatoid or specific infectious arthritis. These joint diseases, we should bear in mind, do cause sufficient joint damage so that subsequent wear and tear changes in these altered structures lead to premature development of well marked hyper-

trophic changes Without the clinical history, the roentgenologist could not be expected to make the correct diagnosis

The finding of arteriosclerosis at the age of 28 bears out the finding of others^{24, 25} that arteriosclerosis appears at an earlier age in gouty subjects

LABORATORY DATA

Hemoglobin (Tallquist) 90 per cent Red blood cell count 4,560,000, white blood cell count 15,000 The differential leukocyte count showed 78 per cent polymorphonuclear neutrophils, 16 per cent lymphocytes and 6 per cent large mononuclear cells The maximal urine concentration observed was 1 012 The urine specimens contained neither albumin, sugar, nor diacetic acid The sediments were negative except for occasional leukocytes and hyaline casts Stool examinations were negative The Hinton test was negative A gonococcus complement fixation test was negative The sedimentation rate (Ernstene-Rourke method⁴⁷) was 0 89 to 1 3 mm per minute, 0 35 mm per minute being the upper limit of normal The serum non-protein nitrogen ranged between 20 and 27 mg per 100 cc The fasting whole blood uric acid was 5 2 to 6 5 mg per 100 cc (Folin method²⁶) for which the upper limit of normal is 5 0 A fractional intravenous phenolsulphonephthalein renal function test showed a 13 per cent excretion in the first 15 minutes, 10 per cent in the second 15-minute period and 23 per cent in the second half-hour, a total of 60 per cent This, according to Chapman's²⁷ data, indicates definite kidney impairment The bromsulphthalein liver function test was normal The blood cholesterol values were always normal Fasting gastric analysis revealed no free hydrochloric acid After histamine injection it reached 15 The arterial-venous sugar tolerance curve after the ingestion of 100 grams of glucose was as follows

	Arterial	Venous
Fasting	96	97
One-half hour	166	153
One and one-half hours	242	218
Three hours	159	146
Four hours	100	97

No glycosuria was observed during the test

COMMENT ON LABORATORY DATA

A mild to moderate leukocytosis is always observed in patients with gouty arthritis Evidence of mild renal impairment such as found in this case is not an infrequent finding in gouty patients^{16, 25, 28} Many of them die of uremia²⁸ Therefore, one should remember the statement "chronic arthritis associated with distinct renal impairment suggests gout until proved otherwise"¹⁶ Urinary gravel and renal stones were present in 12 of 100 cases¹⁶ Achlorhydria appears to be no more frequent in gouty patients than in other individuals An abnormal peak type of sugar tolerance curve such as seen in this patient has been observed in other gouty patients as well as in patients with rheumatoid arthritis³² That this is of no diagnostic significance is shown by the fact that in other individuals with the same types of joint disease normal sugar tolerance curves are observed We have frequently observed an increased sedimentation rate in gout³² In several instances the rates have been as high as 2 0 mm per minute Such increases

are not necessarily related to alterations in the serum proteins because in several instances they have been noted in subjects having normal serum albumin and globulin values³²

SUBSEQUENT COURSE

During his hospital stay, the patient experienced numerous attacks of arthritis, varying considerably in severity (figure 1). Some were extremely mild (+), others quite disabling and extremely painful (++++) One such attack lasted two weeks, involved most of his joints and was accompanied by a temperature of 103.5° F (rectally) at times. Such attacks always responded very promptly to colchicin (grains 1/120 every 1½ hours), provided it was given until toxic symptoms (nausea, vomiting and diarrhea) appeared. Eight such tablets were usually necessary. The course of his gout and of the hyperuricemia was not materially influenced by a low purine diet over a period of three months.²⁹ The severity and frequency of his attacks while on a low purine diet did bear a relation to the urinary uric acid concentration (table 1).

TABLE I

Showing the Relationship Between the Uric Acid Excretion and the Attacks of Arthritis				
Date	Urine Volume c c	Uric Acid Excretion mg	Uric Acid Concentration of mg per 100 c c Urine	Symptoms
1/28/35	1540	580	37.6	0
1/29/35	1380	670	48.5	0
1/30/35	1450	1040	71.7	+
1/31/35	1730	1250	72.2	++
2/1/35	1920	2180	113.5	++
2/2/35	1680	2180	129.7	+++
2/3/35	1510	1890	125.0	+++
2/4/35	1730	1730	100.0	++
2/5/35	1960	1380	70.4	+
2/6/35	1890	1270	67.1	+
2/7/35	2130	1100	51.1	++
2/8/35	1840	1220	66.3	++
2/9/35	1790	1040	58.1	+
2/10/35	1630	670	41.1	+
2/11/35	1750	980	56.0	+
2/12/35	1910	750	39.2	+
2/13/35	1760	810	46.0	0
2/14/35	1750	880	50.2	0
2/15/35	2070	940	45.4	0
2/16/35	1760	990	56.2	0
2/17/35	2170	1140	52.5	0
2/18/35	1770	850	48.0	0
2/19/35	2000	830	41.5	0
2/20/35	1810	980	54.1	0

The patient was on a low purine diet during this period. We are indebted to Drs. Jacobson and Talbott of this clinic who made these determinations.

His treatment during these first two hospital stays was directed toward correction of the deformities. This was attempted by means of various types of splints and casts and operative procedures* in conjunction with exercises.

The olecranon bursa was subsequently removed (specimen I). It was filled with white, chalky material. Typical monosodium urate crystals giving a positive murexid

*The biopsies and operations were performed by Drs. F. A. Simeone, G. W. VanGorder and Sumner Roberts.

test were readily demonstrated. In order to determine with absolute certainty that the ankylosis was due to gout and not to a co-existing rheumatoid arthritis, the patient consented to a biopsy of his left ankle and foot. Biopsy specimens were removed from the ankle (specimens II and III) and the scaphoid-cuneiform joints (specimen IV). It is interesting in connection with this point that the patient's serum did give positive agglutination tests for hemolytic streptococci (Strains NY₅ and C₁₇) on several occasions. In one instance the titer was 1/1280. On other occasions, however, such agglutination tests were negative.

At a later date the patient requested amputation of the head of the proximal phalanx of the third finger in order to correct the hyperextension deformity as well as to give him a movable joint (specimen V). In order to overcome the flexion deformity of the right knee, a capsuloplasty was done. The tissue removed at the time of this operation represents specimens VI and VII. All the biopsy specimens are described in detail under pathological findings.

This patient has been under constant observation since his initial hospital entry. Studies pertaining to his hyperuricemia have been reported in this same volume (Case 2) by Jacobson.²⁹ Further detailed metabolic studies, similar to those previously reported³⁰ have been made by Dr. J. H. Talbott and will be reported in future publications.

COMMENTS ON SUBSEQUENT COURSE

Except for one serum uric acid value of 5.2 mg per 100 c.c. (following a salyrgan diuresis), this patient has always exhibited a fasting hyperuricemia of 6 or more mg per 100 c.c. of serum.²⁹ During as short a period as seven weeks, Jacobson made 33 fasting serum uric acid determinations on this patient.²⁹ These 33 values varied between 7.4 and 14.5 mg per 100 c.c. The patient received no treatment during this period. Jacobson also presents the serum uric acid variations encountered during a period when the patient was having attacks of gouty arthritis as compared with an attack-free period. In each instance the patient was on a low purine diet without other therapy. Of 13 determinations made during a period with arthritis, the fasting serum uric acid varied from 10.5 to 14.5 mg per 100 c.c. with a mean value of 12.4 ± 2.0 , whereas during the arthritis-free period, 20 determinations were found to vary from 7.4 to 13.6 with a mean value of 12.1 ± 3.0 .

Of the 177 fasting serum uric acid determinations made on 21 untreated gouty subjects Jacobson found that 174 or 98 per cent exceeded a value of 6 mg per 100 c.c. Ninety-four per cent or 167 exceeded a value of 7 mg per 100 c.c. Our experience with a larger series of gouty subjects³² on whom less frequent determinations have been made is the same, namely, that the fasting serum uric acid value of untreated gouty patients whether free of arthritis or not has always been 6 mg per 100 c.c. or over. From these data, it would appear that a hyperuricemia is practically if not always present in untreated presumptive or tophaceous gout. There may well be exceptions to this rule but if so they have not been encountered in this clinic.^{29, 30, 31, 32} Jacobson was unable to prove that the same change in the serum uric acid always preceded the attack of the arthritis. From his data it would seem that it might vary considerably from individual to individual.

and from attack to attack. In some instances it was unchanged, in others decreased or elevated. Various workers report lowering of the uric acid following treatment. It is hazardous to draw such conclusions unless the possible variations in any one subject have been well established by daily determinations over a period of seven to ten days prior to the institution of said therapy. If such control studies are not made on each patient treated, one may interpret lowering of the serum uric acid as having resulted from the treatment, whereas it may represent nothing more than the naturally occurring variations of that particular individual. Until such well controlled metabolic studies with various types of treatment have been made, we will not know the correct answer to such questions.

We are of the opinion that the requirements for uric acid determinations laid down by Talbott and Jacobson^{29, 30, 31} must be adhered to if we are to obtain comparable values giving the smallest possible variations. These are: Drawing of the fasting blood under oil, transferring it to a tube under oil, allowing it to clot, centrifuging and transferring the necessary amount of overlying serum to an Erlenmeyer flask. One can employ either the Folin³⁶ or the Benedict³⁷ method.

From table 1, it will be seen that the concentration of uric acid per 100 c.c. of urine while on a low purine diet was always greatest at the time of arthritic symptoms. A normal individual rarely excretes more than 0.6 gram per day^{24, 25}. The average daily excretion for 20 gouty patients was 0.25 gram^{24, 25}. As Pratt points out "probably 5 per cent of gouty patients have a uric acid excretion which is either a high normal or supernormal"²⁵. In this instance, a high uric acid excretion was possible even though slight renal impairment was present.

The treatment for the acute attacks of arthritis in this case has rarely been other than colchicin. This drug is practically a specific for acute gouty arthritis. It should be administered in pill form, grains 1/120 every one or two hours until nausea, vomiting, and diarrhea appear. It is then discontinued. Freedom from pain and subsidence of swelling occur within 24 to 72 hours. The diarrhea is usually sufficiently severe to require treatment with paregoric or bismuth subnitrate. Once the patient has established the amount necessary to produce such symptoms, he can reduce the total dose by 1 or 2 pills and still accomplish the desired effect. Occasionally opiates are required, though rarely if colchicin is administered as soon as the first warning symptoms appear. The patient should always carry his colchicin with him. Besides such therapy for the acute arthritis, we advise avoidance of the few high purine-containing foods and known precipitating factors, a high fluid intake and large doses of aspirin 60 to 80 grains four days out of every week. We never employ cinchophen because of the risk of inducing acute yellow atrophy and the fact that the pill form of colchicin is equally if not more efficacious. We are doubtful if this or any other regime of therapy materially affects the course of the disease. Again, one

must proceed with caution and have conditions extremely well controlled before concluding that the frequency, duration and severity of the arthritic attacks have been materially influenced. We must bear in mind the natural course of the disease, the natural interval of time between attacks and that the attack of arthritis is usually self-limited.

The necessity of employing certain medical orthopedic measures, such as some physiotherapeutic procedures, aspiration of effusions, immobilization in casts, correction of deformities by casts and operations, etc., must be borne in mind.

PATHOLOGICAL EXAMINATION

Specimen I (The olecranon bursa) It measured 2 by $1\frac{1}{2}$ by 1 cm. A soft, grayish-white, chalky material was easily expressed from freshly made sections. Microscopic examination revealed numerous, varying sized deposits of a non-cellular, lightly staining, foreign material. Under high power magnification this material was seen to consist of masses of needle shaped crystals. Many of these deposits were partially surrounded by foreign body giant cells, mononuclear leukocytes, lymphocytes, and plasma cells. Focal areas of heavy mononuclear inflammatory cell infiltration were also observed.



FIG 11 Photomicrograph of low magnification ($\times 10$) showing fibrous ankylosis of the astragalotibial joint. The cancellous bone of the astragalus is shown in the upper portion of the photograph. Small strips of eroded articular cartilage adjacent to the astragalus represent the only remaining articular cartilage. Note the numerous light areas (arrows) in the connective tissue that have replaced the joint space. These are monosodium urate crystals. They are surrounded by zones of marked chronic inflammation. Celluloidin section stained with hematoxylin and eosin.

Specimen II (Biopsy of astragalotibial joint) The specimen measured $1\frac{1}{2}$ cm in length and 7 mm in width. Near one margin of the specimen was a plate of

cartilage, representing the astragalotibial articulation. This measured 3 mm in thickness and was bounded on either side by cancellous bone. Sections from this specimen showed a large area of cancellous bone from the astragalus. The overlying articular cartilage was covered by a thick layer of dense, moderately vascular, heavily infiltrated fibrous tissue (pannus). Extremely numerous urate deposits were present throughout this layer of pannus. Most of the urate deposits were of small size. They were surrounded by a heavy infiltration of mononuclear phagocytes and foreign body giant cells. Occasional larger deposits were observed. Numerous focal areas of dense lymphoid cell infiltration were present. The intervening connective tissue was moderately heavily infiltrated with lymphocytes, mononuclear leukocytes and polymorphonuclear leukocytes.

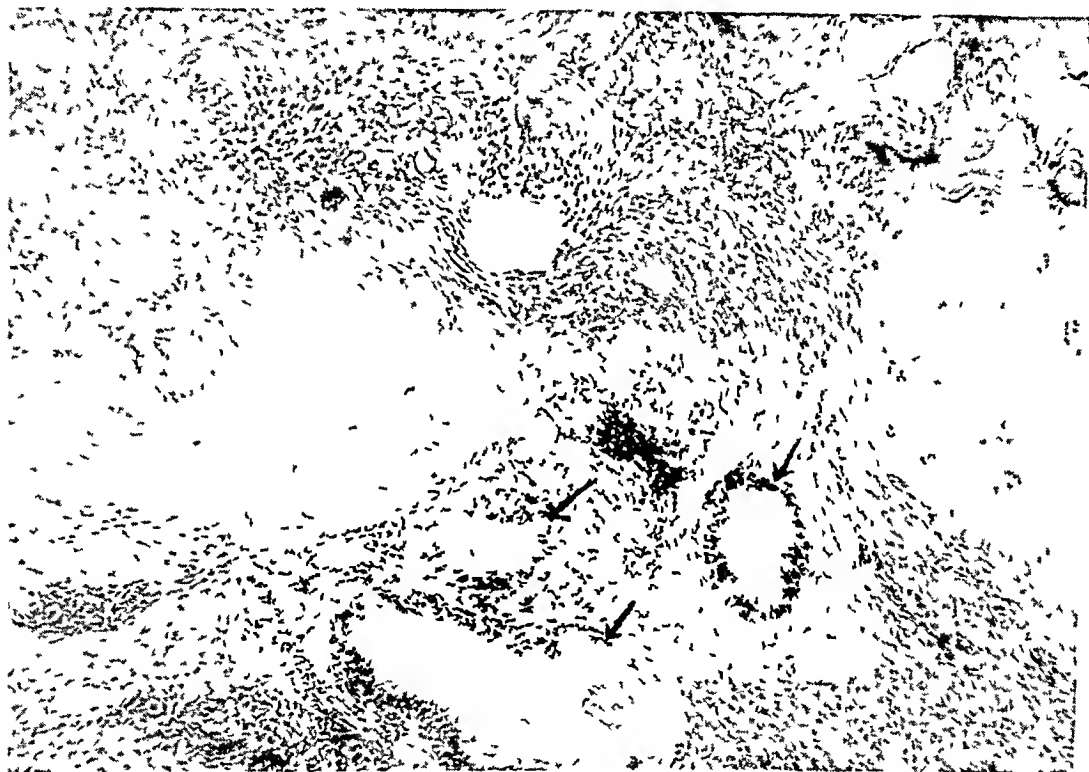


FIG 12 A higher power photomicrograph of area outlined in the above photomicrograph. Note the invasion of articular cartilage by fibrous tissue, the areas of sodium urate deposits (arrows) and the adjacent inflammatory cell infiltration of the tissues. Magnification $\times 100$.

The underlying cartilage contained numerous small pits. These represented areas of destruction due to the invasion by the very cellular, vascular pannus tissue. In most instances such depressions contained one or more masses of urate deposits. Additional evidence of injury to the articular cartilage was exhibited by the absence or diminution in the number of cartilage cells in the more superficial areas as well as by irregularities in the matrix of the cartilage surface directly beneath the pannus. In a few areas complete destruction of the cartilage had resulted and the heavily infiltrated vascular connective tissue had penetrated the calcified zone of cartilage and extended into the subchondral bone spaces of the astragalus.

Specimen III (Biopsy of astragalotibial articulation). In this specimen, the astragalotibial joint space was replaced by a 3.5 mm band of fibrous tissue. The

entire specimen measured 1.2 by 1 cm. The histological changes observed were very similar to those seen in specimen II, except that both bones entering into the articulation were shown. These were firmly united by a dense, moderately vascular fibrous tissue (fibrous ankylosis). The subchondral bone spaces were extensively invaded by connective tissue, infiltrated with numerous inflammatory cells. The remaining cartilage consisted of small irregular fragments which were completely surrounded by fibrous tissue (pannus). Urate deposits were very numerous throughout the fibrous tissue which had replaced the joint space (figures 11 and 12).

Specimen IV (Biopsy of the scaphoid-cuneiform joint). It measured $1\frac{1}{2}$ by 0.7 cm in its greatest dimensions. It included one peripheral margin of the scaphoid and cuneiform articulation. One section through this articulation showed no abnormalities in the subchondral bone except at the extreme margin of the joint. In this region, urate deposits were observed in a few of the marrow spaces of the bone on either side of the joint. Such urate deposits were surrounded by heavy inflammatory cell infiltration including foreign body giant cells. One also noted considerable vascular fibrous tissue replacement of the bone marrow tissue wherever

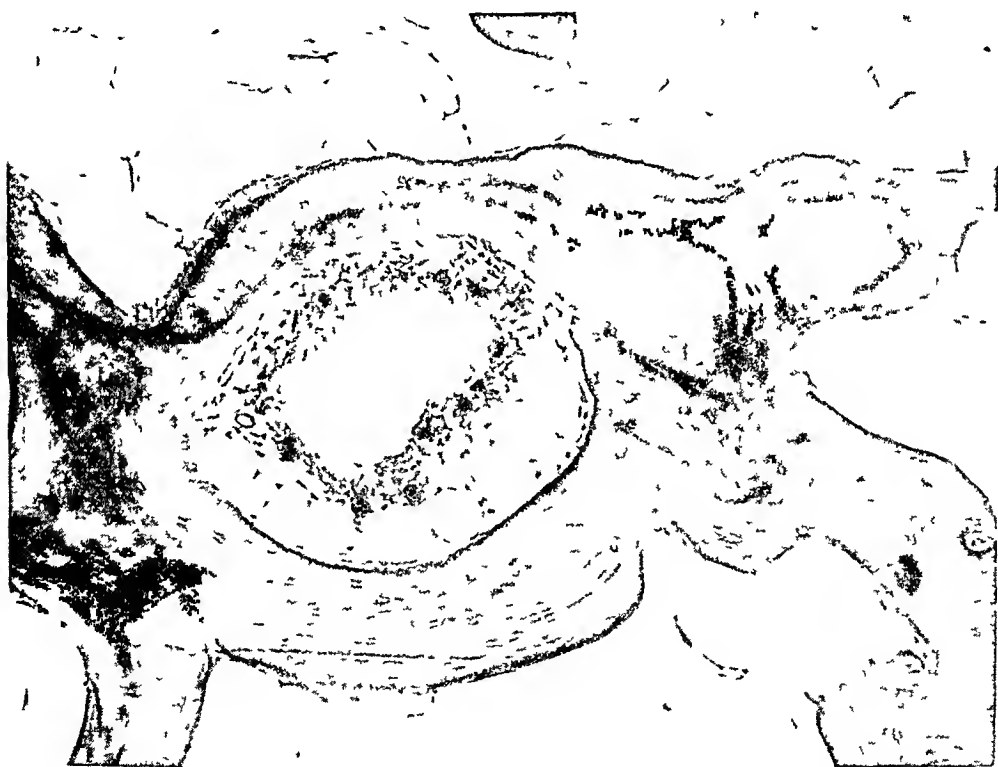


FIG 13 An isolated urate deposit deep in the cancellous bone of the finger illustrated in the following photomicrograph. Examination of serial sections proved that this and other deposits of sodium urate were entirely within cancellous spaces of the subchondral bone. Celloidin section—hematoxylin and eosin stain. Magnification $\times 100$.

urates had been deposited. The overlying cartilage in these areas had been completely destroyed, suggesting that the invading urate-containing fibrous tissue had come from the joint space. However, we could not be certain because the joint capsule in this region was likewise the site of urate deposits and marked proliferation.

Elsewhere in the section the articular cartilage was thinned out and very irregular in contour. Urate deposits unaccompanied by pannus were observed on both articular

surfaces Extensive degeneration of the remaining cartilage was present as shown by the absence of many of the cartilage cells and marked fibrillation of the remaining matrix No appreciable amount of pannus was found on the remaining articular surfaces

Specimen V This consisted of the head of the proximal phalanx of the right third finger and several small fragments of the articular capsules The articular cartilage was gray and non-glistening, measuring approximately 1 mm in width Its surface was uneven because of numerous pits The head of this proximal phalanx was divided in the mid-line Serial sections were cut from each block towards the periphery of the specimen This was done in order to demonstrate whether the deposition of urates in the subchondral bone spaces was primary or the result of urate-containing pannus penetrating through the articular cartilage Because of the extensive nature of the lesions, it was impossible to answer this point with absolute certainty However, the occurrence of isolated urate deposits (figure 13), deep in the subchondral bone spaces, and the occurrence of small deposits on the surface of the articular cartilage was interpreted as strong evidence that the destructive lesions about the joints can be due to either This is what one would expect in a metabolic disease The uneven articular cartilage surface was again due to superficial urate deposits and the accompanying degeneration of the cartilage cells and matrix In addition, one noted large circular defects extending through the entire thickness of articular cartilage into the underlying subchondral bone (figure 14)



FIG 14 Photomicrograph ($\times 10$) showing the articular end of the proximal phalanx of the third left finger The free surface of the articular cartilage is frayed and uneven Cartilaginous and bony overgrowth (lipping) is present at the articular margins Two large circular defects (punched-out areas) are present in the articular cartilage and subchondral bone These lesions are lined by fibrous tissue which is infiltrated with large numbers of inflammatory cells and studded with numerous masses of sodium urate crystals Note the isolated urate deposits in the bone marrow (arrows) Celloidin section stained with hematoxylin and eosin

These defects were filled with large masses of urate crystals, which were surrounded by heavily infiltrated sheaths of connective tissue The adjacent bone trabeculae showed evidence of moderate lacunar absorption In some areas the histological

appearances suggested that following extensive undermining of the calcified zone of cartilage, collapse of the overlying articular cartilage had taken place (figure 14) Cartilaginous and bony overgrowth was present at the articular margins

Specimen VI It consisted of a piece of capsular tissue from the knee joint Microscopic examination revealed that it was studded with large and small foci of urate crystals Such urate collections were surrounded by a cellular zone containing numerous mononuclear cells having the appearance of epithelioid cells Lymphocytes, eosinophiles and occasional giant cells were also present In the areas free of urate deposits the tissues consisted of extremely dense contracted fibrous tissue

Specimen VII A small strip of articular cartilage from the posterior aspect of the femoral condyle It was greatly reduced in thickness Its surface was extremely uneven The perichondrial margin was covered by a thick layer of fibrous tissue The cartilage itself contained numerous small urate foci The irregular surface pits and depressions were covered by urate deposits The cartilage matrix was fibrillated, the cells unevenly arranged, in many regions being grouped in clumps

COMMENT ON PATHOLOGICAL EXAMINATIONS

The evidence that gout is a metabolic disease is quite convincing The fact that one can, with persistence, obtain a positive family history in a high percentage of cases is of itself extremely good evidence that it is probably an inborn disease of metabolism Further studies on the children of gouty patients will give further evidence in this direction Its occurrence in women is rare^{3, 5, 9, 16, 24, 25} Irrespective of the various metabolic alterations observed in such patients, one fact remains, namely, that the pathological changes observed in gout are secondary to the deposition of monosodium urate Urate tophi are the only known specific lesions of gout This is true of the cutaneous, articular and visceral structures, and possibly the vascular sclerosis as well, because such sclerotic lesions are readily demonstrated in the region of urate deposits, and accompanying the heavily infiltrated vascular fibrous tissue about them The factors which govern the diffusion of urates into the various tissues are as yet unknown Once they become extravascular, they serve as foreign body irritants in consequence of which proliferation occurs We do not know the factors responsible for the more frequent deposition of urates in the articular and subcutaneous tissues It is true that visceral tophi have been observed, but many of the reported instances can hardly be considered authentic because urate crystals or a positive murexid test was not demonstrated We know of one instance of a tophus in the tongue⁴⁰ and tophi occurring in the heart muscle have been described^{41, 42, 43, 44, 45}

In this particular case urate crystals were demonstrated in the tophi of the ear, olecranon bursa and the finger They were also observed in the cartilage, the synovial membrane, the periarticular fibrous tissue and in the subchondral bone spaces of the various joints biopsied

The articular changes encountered in gout are dependent upon the amount of monosodium urate deposited, its location and the resulting reaction to such depositions

From the observations in this case, it is apparent that articular deformity may result because of extensive fibrosis of the periarticular tissues subsequent to the urate deposition, thus producing contractures and limitation of motion

If such deposition occurs in the synovial membrane or subsynovial tissues, the resulting proliferation may be sufficiently marked to produce extensive pannus which in turn may completely cover the articular cartilages and cause a true fibrous tissue ankylosis not unlike that seen in rheumatoid arthritis. Such joints can subsequently go on to true bony ankylosis^{8, 9, 12, 14, 46}. The pannus may invade or completely destroy the articular cartilage and calcified zone of cartilage with subsequent invasion of the subchondral bone spaces with destruction of the bone trabeculae. These changes lead to the typical punched-out areas seen on the roentgenograms. The pannus in gout differs from that of rheumatoid arthritis in that one can always demonstrate islands or masses of urate crystals in the pannus, provided the tissues are placed in special fixatives. It would appear that if urate deposition occurs primarily in the subchondral spaces, the accompanying vascular infiltrated fibrous tissue proliferation may be sufficiently marked to destroy bone trabeculae and produce the same typical punched-out areas previously described.

Deposition of urates confined solely to the articular cartilage will result in marked cartilage changes such as thinning, pits, depressions, fissures, crevices, diminution in number, scattering and clumping of cartilage cells. From the observations in this case, it is apparent that urate deposition in the articular cartilage can be sufficiently injurious to explain the development of degenerative joint disease or hypertrophic arthritic changes³³ of a more advanced character than would ordinarily be encountered in an individual this age^{33, 34, 35}. Such changes were very marked in the knees of this patient (figure 8). The degenerative joint changes are in direct relation to the extent of the urate deposition and not merely an expression of long-continued use and increasing age. Therefore, we must appreciate that the deposition of monosodium urate in the articular cartilage can be responsible for the early appearance of extensive degenerative joint disease changes.

From what has been observed in this case, it must be apparent that all the described pathological changes may occur in any one joint.

Changes such as were encountered in this case have been reported previously^{6, 7, 8, 9, 10, 11, 12, 13, 14}. Virchow in 1868⁶ described a case of gout in which complete fibrous ankylosis of the phalangeal joint of the great toe took place. He stated that urate deposits were to be found not only in the cartilages, the thick layers of the periosteum, and the ligaments, but also in the fibrous tissue obliterating the joint space, within the joint itself. Isolated foci of uratic deposit were also seen in the marrow spaces of spongy bone. In 1876, Litten¹⁵ described a very severe case of gout in a patient of 41, in whom the first attack had presumably occurred at the age of eight

The hips, knees, shoulders, right elbow, wrists, fingers, and toes were all completely or partially ankylosed. In the large joints, the synovial membrane, the fibrous capsule, the ligaments, and the cartilages were all found to be covered with a thick layer of white, shiny urates having the consistency of ointment. The semilunar cartilages of the knees were almost completely destroyed. In the cartilages, the urate deposits were found exclusively in the intercellular substance, in decreasing amounts toward the epiphyseal border. The ankyloses were regarded as fibrous ankyloses with deformity and shrinking of the synovial capsule. A number of foci of urate deposits were found in the spongy bone of the epiphyses, as well as in the epiphyseal periosteum and perichondrium. In addition, urate deposits were present in the kidneys to a marked degree. The larynx was involved in the same manner. Amyloid deposit was noted in the arteries of the spleen, and amyloidosis of the kidneys was present. Although all of these changes have more recently been described in great detail in single joints by Pommer² and Brogsitter,¹⁴ it is important to appreciate that generalized ankylosis due to gout is rare.

Certain authors have reported that rheumatoid arthritis and gouty arthritis are occasionally encountered in the same individual^{38, 39}. The proof presented is anything but convincing. In all such instances, biopsies should be obtained if possible. This is the only means by which one can prove or disprove such a statement. In this case there were many aspects (particularly the physical and roentgen-ray findings) which closely resembled rheumatoid arthritis. In addition, positive streptococcal agglutination tests were obtained on a number of occasions. Some workers might consider such evidence sufficient to make a diagnosis of rheumatoid arthritis, yet biopsy of four joints demonstrated very clearly that the joint changes present were due solely to the deposition of urates in the periarticular tissue, synovial membrane, subsynovial tissue, cartilage and subchondral bone spaces. Without the biopsies, it would have been extremely difficult for us to prove that the joint deformities and ankyloses were due to gout.

This case serves to emphasize the fact that widespread ankylosis due to gout is occasionally encountered. It also illustrates another point, namely, that if one becomes gout-conscious, the incidence of gout seemingly increases. This increase, however, is directly related to one's knowledge of the disease. As it increases, so does the incidence of gout. If one is to demand the presence of tophi, characteristic roentgen-ray changes and hyperuricemia before making the diagnosis of gout, many cases of "presumptive" gout will go on for years undiagnosed or mislabelled. Our interest in this disease was aroused some years ago by the insistence of Hench that cases of "presumptive" gout are frequently not recognized. That such an assumption was correct has been borne out. Increasing suspicion of its existence has resulted in a marked increase in the number of cases so diagnosed in this clinic each year. This experience is similar to that of Hench.⁴⁸

SUMMARY

1 The findings in a severe case of gout with rapidly appearing widespread ankylosis are presented

2 Many of the clinical features resembled those seen in an individual with advanced rheumatoid arthritis

3 The diagnosis of gout in this case was confirmed by demonstrating monosodium urate crystals in the tophi of the ear, the finger and the olecranon bursa They were also demonstrated in the periarticular structures, synovial membrane, subsynovial tissue, subchondral bone spaces and articular cartilage of the four joints examined

4 The histological changes seen in the astragalotibial joint simulate those seen in advanced rheumatoid arthritis except that the pannus responsible for the complete fibrous ankylosis contained innumerable urate deposits Such urate deposits induce marked proliferation of the synovial and subsynovial tissue (pannus) Once this has formed, the ensuing changes take place rapidly

5 Urate deposits in the articular cartilage resulted in sufficient articular cartilage damage to allow marked degenerative joint changes (hypertrophic arthritis) to appear at a much earlier age than they are ordinarily encountered

6 The differential diagnosis of acute, recurrent gouty arthritis is discussed

7 The clinical features of "presumptive" gout are presented in detail with the hope that more physicians will be made gout-conscious

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THE URIC ACID IN THE SERUM OF GOUTY AND OF NON-GOUTY INDIVIDUALS ITS DETER- MINATION BY FOLIN'S RECENT METHOD AND ITS SIGNIFI- CANCE IN THE DIAG- NOSIS OF GOUT¹

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SINCE the original description by Folin and Denis¹ in 1913 of a colorimetric method for the estimation of uric acid in blood, and the application of this method in the same year by Pratt² to the study of gout, scores of publications have concerned themselves with both methods and with blood uric acid values in health and disease. To review this vast literature completely would serve no purpose, especially as many divergent results have had as their basis methods of estimation fraught with various sources of error. The present communication describes the use of the most recent Folin method in the study of a number of gouty and of non-gouty individuals. In substance the results of this study constitute an amplification and confirmation of the earlier findings of Pratt².

THE DETERMINATION OF URIC ACID IN SERUM

Since the spring of 1933 the latest Folin³ method for the determination of blood uric acid has been in use in this laboratory. In the course of the application of this method to the study of gouty patients the procedure has been adhered to with but one minor modification to be described below.

In his last paper Folin³ recommended the use of improved reagents on unlaked whole blood filtrates. He had previously⁴ proposed the use of unlaked blood filtrates in order to avoid the presence of substances which inhibit the color reaction, and of reactive, non-uric acid substances, both of which are apparently set free from laked blood cells. The unlaked blood filtrates were thought to contain the readily diffusible products of the blood cells, but were supposedly free of disintegration products of the cells. With the improvement in the sensitivity and specificity of the reagents Folin believed that the problem of the accurate determination of uric acid in small quantities of blood had been satisfactorily solved.

Early in the course of this work, on the suggestion of the late Professor

* Received for publication August 16, 1937

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A considerable part of this work was carried out during a collaborative study of gout by Dr. John H. Talbott of this clinic, and the author

Folin, we estimated the uric acid in both whole blood and in plasma of the same sample. During frequent determinations of the blood uric acid in one case of gout, it soon became apparent that the whole blood values, measured in strict accordance with Folin's directions, exhibited a degree of fluctuation far greater than the variation in simultaneously determined plasma uric acid values. The method of handling the blood has been

TABLE I
Uric Acid Extracted from Red Blood Cells

Blood Number of Sample	I Uric Acid, Plasma, Observed, mg per cent	II Uric Acid, Unlaked Whole Blood, mg per cent	III Cell Volume, per cent	IV Plasma Volume, per cent	V Uric Acid, Plasma, Calculated, mg per cent	VI Uric Acid, Extracted (V-I), mg per cent
1	8.27	4.61	48.30	51.70	8.90	0.63
2	8.73	5.53	42.65	57.35	9.64	0.91
3	9.44	6.38	43.40	56.60	11.3	1.86
4	9.68	5.80	45.00	55.00	10.6	0.92
5	9.78	5.84	44.65	55.35	10.6	0.82
6	9.86	6.20	43.55	56.45	11.0	1.14
7	9.90	6.64	48.80	51.20	13.0	3.10
8	10.0	6.90	45.95	55.05	12.5	2.50
9	10.5	6.37	45.50	55.50	11.5	1.50
10	10.5	6.83	41.24	58.76	11.6	1.10
11	10.6	7.05	40.10	59.90	11.8	1.20
12	10.8	6.50	47.00	53.00	12.3	1.50
13	10.9	6.20	48.90	51.10	12.1	1.20
14	11.1	7.28	42.20	57.80	12.6	1.50
15	11.2	7.48	43.95	56.05	13.4	2.20
16	11.2	6.76	45.40	54.60	12.4	1.20
17	11.4	6.66	47.80	52.20	12.8	1.40
18	12.3	7.00	46.40	53.60	13.1	0.80
19	12.4	7.84	47.40	52.60	14.9	2.50
20	12.4	7.80	45.00	55.00	14.2	1.80
21	12.5	8.48	41.62	58.38	14.5	2.00
22	12.8	9.67	44.80	55.20	17.5	4.70
23	13.1	7.35	48.25	51.75	14.2	1.10
24	13.3	7.42	42.70	57.30	13.0	-0.30
25	13.3	7.93	47.00	53.00	15.0	2.70
26	13.4	8.96	42.30	57.70	15.5	2.10
27	13.5	9.32	47.82	52.18	17.9	4.40
28	13.9	10.1	51.00	49.00	20.6	6.70
					Average	1.97

previously described.⁵ In brief, the venous blood, drawn without stasis from the subject under basal conditions, was treated with heparin and was then equilibrated with carbon dioxide at a tension of approximately 40 mm of mercury.* The equilibrated whole blood was then centrifuged under oil, and the plasma separated. Samples of both equilibrated whole blood and plasma were taken for analysis. Such analyses of 28 different blood samples, all from a patient suffering from gout, are given in table 1.

* The author is indebted to Dr. John H. Talbott for carrying out the equilibrations.

These data demonstrate that with increasing plasma uric acid values the concentrations of whole blood uric acid do not increase regularly. We might assume, as Folin apparently did, that the uric acid determined in unclotted whole blood represents the uric acid in the plasma together with uric acid that has diffused from the red blood cells. If this assumption be true it would be expected that the determined values of plasma and whole blood uric acid would run parallel, inasmuch as uric acid appears to be freely diffusible between plasma and cells⁶. The data of columns I and II of table 1 do not show the expected parallelism. Knowing the plasma volumes it is possible to calculate, from the value of the whole blood uric acid, the concentration of uric acid in the plasma*. Such calculations are presented in column V of table 1. It is evident that in every case but one (sample 24) the calculated *exceeds* the observed value of plasma uric acid concentration. The deviations of the calculated from the observed values are listed in column VI of table 1. It is seen that the deviations bear only a rough relation to the magnitude of the observed plasma uric acid values, the smallest being 0.63 mg per cent, and the largest 6.7 mg per cent. These deviations, which are obviously due to the extraction from the red blood cells of uric acid or of reactive, non-uric acid substances, are *variable* in magnitude, and determine the extreme variation of whole blood uric acid values among the samples with approximately equal plasma uric acid concentrations.

There appeared to be at least two possible explanations of the variable additional quantities of uric acid found in the whole blood samples. In the first place, although a sample of equilibrated whole blood was used for the determination, the handling of the specimen, fresh from the tonometer, involved rapid stirring in the atmosphere, pipetting of 1 c.c. from the sample into a 25 c.c. Erlenmeyer flask, and agitation after the addition of the sodium tungstate solution. It is obvious that this repeated exposure to the atmosphere of the sample resulted in a loss of carbon dioxide from the blood, and rendered it essentially non-equilibrated whole blood. The following experiment demonstrated the effect of the loss of carbon dioxide upon the apparent uric acid value. A sample of whole blood from a gouty individual was divided into two parts, one part stirred with heparin in an open vessel, the other part similarly treated under a layer of mineral oil. One c.c. of the latter portion was transferred under oil to the Erlenmeyer flask, and the protein was precipitated under oil. The whole blood uric acid in the portion exposed to the air measured 7.6 mg per cent, while the portion handled anaerobically yielded a value of 6.8 mg per cent. Differences in the same direction are shown by the data of table 2. In these experiments each sample of whole blood was divided into two parts, one part allowed to clot in a centrifuge tube under a layer of mineral oil, the other part in a centrifuge tube without oil, with both tubes kept at 4° C.

* Calculated plasma uric acid = whole blood uric acid X 100/plasma volume

TABLE II
Uric Acid in Serum

Blood, Number of Sample	Serum of Blood Clotted under Oil, Uric Acid, mg per cent	Serum of Blood Clotted in Air, Uric Acid, mg per cent
1	10.5	11.0
2	10.3	10.8
3	10.0	10.6
4	9.7	10.1
5	7.7	7.7

for approximately $1\frac{1}{2}$ hours. It was thus evident that exposure of the blood to the atmosphere, in four of five experiments, increased the apparent uric acid content, *not only of the whole blood, but also of the serum*. On the other hand, when precautions were taken to minimize the exposure of the blood samples to the air there were obtained serum uric acid values practically identical with those of plasma of the same *equilibrated* samples. In table 3 are presented data which indicated that allowing the blood to clot

TABLE III
Comparative Uric Acid Concentration in Plasma and Serum

Blood, Number of Sample	Plasma of Equi- librated Blood, Uric Acid, mg per cent	Serum of Blood Clotted under Oil, Uric Acid, mg per cent
1	12.6	12.0
2	11.6	11.6
3	11.2	11.4
4	10.5	10.5
5	10.1	10.2
6	6.7	6.6

under a layer of oil furnished serum uric acid values which closely approximated those of plasma that had been separated from the red blood cells under a physiological tension of carbon dioxide. On the basis of the fore-going data, therefore, wherever serum rather than plasma from equilibrated blood has been used, the serum has been derived from a sample of whole blood that has been allowed to clot under a layer of mineral oil. The blood was drawn into an oiled syringe, immediately thereafter the tip of the needle was inserted under the surface of a few cubic centimeters of mineral oil contained in a centrifuge tube, and the blood was then expelled under the oil. All of the uric acid values described below are based upon analyses of such sera, or of plasma of equilibrated blood.

That this apparent increase in uric acid content accompanying the slight loss of carbon dioxide depends upon a migration of uric acid or of reactive, non-uric acid substances, from the blood cells into the serum as the blood becomes more alkaline is suggested by the experimental data of Jacoby and

Friedel⁷ These authors studied the loss of uric acid from the plasma after the addition of known amounts of uric acid to whole blood maintained by phosphate buffers at pH 7.38, 7.17, and 6.46, respectively. In every one of 13 such experiments an increase in the pH was accompanied by greater recovery in the plasma of the added uric acid. A shift in the same direction of both native and of added uric acid has more recently been reported from this clinic by Talbott and Sherman⁶

A second explanation of the variable increments of whole blood uric acid, over the calculated values of plasma content, was the possibility that the reagents used in precipitating the unlaked blood cells might extract from the cells uric acid, or reactive non-uric acid substances. This possibility has been rendered probable by the work of Heller⁸. He showed that *variable* amounts of uric acid (or of chromogenic material) could be washed out of the blood cells by the hypertonic sodium tungstate solution, and that additional but *inconstant* amounts were extracted during acidification with the sulfuric acid. The averages of a number of determinations were 1.32 mg per cent extracted by the sodium tungstate alone, and 1.85 mg per cent after the addition of the sulfuric acid. This latter value is of the same order of magnitude as the average of the present experiments (column VI, table 1).

Because of these variable degrees of extraction from the blood cells, it seemed desirable to give up whole blood uric acid determinations entirely, and to determine uric acid only in serum in the manner described above. Plasma or serum uric acid determinations have been employed in the past by many investigators, including Folin, Berglund, and Derick,⁹ Thannhauser,¹⁰ and Wiener and Wiener.¹¹

THE RECOVERY OF ADDED URIC ACID

Two procedures have been commonly employed in the past to define the specificity and the accuracy of various methods for the determination of uric acid in blood, namely, a comparison between the results of colorimetry directly upon the blood filtrate with the values obtained after preliminary precipitation of the uric acid, and the extent of recovery of uric acid added to blood. That all of the color developed by the Folin 1933 reagents is probably due to uric acid is suggested by the fact that both the direct and the indirect methods yield practically identical values. In his last paper³ Folin demonstrated that applying the reagents directly to the unlaked whole blood filtrates resulted in values no higher than those obtained after preliminary precipitation with silver nitrate. For this reason all of the values reported below represent *direct* determinations on the serum filtrate.

Throughout the literature concerning the determination of uric acid there have repeatedly cropped up reports of incomplete recoveries of uric acid added to whole blood.¹² The earlier claim of quantitative recoveries made by Folin and Wu¹³ was within three years corrected by Folin,¹⁴ who then admitted that losses of as much as 10 per cent of added uric acid might

be encountered. It was principally because of this incomplete recovery that Folin in 1930⁴ turned to the use of *unlaked* whole blood filtrates, and demonstrated that the loss of added uric acid was not dependent solely upon adsorption of uric acid by the precipitated protein, but rather was due to the fact that something in laked blood filtrates *depressed* the color reaction. This inhibitory effect was apparently completely avoided when unlaked blood filtrates were used, as evidenced by the quantitative recoveries of uric acid added to such bloods⁴. Similarly, data presented by Folin in his last paper³ showed that of uric acid added to whole blood from 94 to 100 per cent was recovered. On the other hand, data are not lacking which indicate substantial losses of uric acid added not to whole blood but to *plasma*. Thus Wiener and Wiener,¹¹ using the Folin 1922 reagents, found the following recoveries of small amounts of uric acid added to plasma: 72, 83, 95, 77, and 100 per cent respectively. Similarly, in the hands of the author the application of the Folin 1933 method to plasma or to serum has not consistently yielded quantitative recoveries of added uric acid. In table 4 are

TABLE IV
Recoveries of Uric Acid Added to Plasma or Serum

Experiment Number	Uric Acid Added, mg per cent	Uric Acid Recovered, per cent of uric acid added
1	3.33	96
2	4.00	61
3		91
4	5.00	80
5		86
6		86
7		86
8		87
9		88
10		92
11		94
12	10.00	87
13		87
14		88
15		88
16		89
17		90
18		91
19		92
20		93
21		93
22		93
23		93
24		95
25		96
26		96
27		97
28		99
29		99
30		102
Average		90

presented the results of 29 experiments. With the exception of one experiment the recoveries were 80 per cent or better, and in 16 experiments the recoveries exceeded 90 per cent. The recoveries could not be consistently bettered by the addition of the uric acid dissolved in the sodium tungstate solution, or by the delivery of the sulfuric acid at an extremely slow rate, with constant stirring of the precipitation mixture. On the other hand, that much of the loss is due to the adsorption of added uric acid by the *precipitated* protein is shown by the following recoveries, after the addition of 10 mg per cent of uric acid *subsequent* to the precipitation of the protein: 96, 89, 99, 98, and 93 per cent, respectively. It must be concluded, therefore, that the present method for the determination of uric acid in serum may involve negative errors of an average magnitude of 10 per cent.

THE SERUM URIC ACID IN NON-GOUTY INDIVIDUALS

The serum uric acid was determined, under basal conditions, in 100 non-gouty adults. All of the subjects had been consuming a mixed diet. In most instances one such value was obtained for each individual, where more than one determination was performed the highest value has been recorded. Among 37 females the mean age was 39.2 years, and among 63 males the mean age was 44.5 years. Of the 100 subjects only 24 were considered free of organic disease. The remaining 76 subjects were hospital and private patients suffering from a variety of, for the most part, chronic diseases. In the choice of these non-gouty patients for the present study there were excluded only those suffering from renal disease with nitrogen retention, disease of the liver, and leukemia, conditions in which it is well established that abnormally high uric acid concentrations may be encountered.

In table 5 are presented the frequency distribution of the non-gouty

TABLE V
Frequency Distribution of Serum Uric Acid Values in 100 Non-Gouty Individuals

Serum Uric Acid, mg per cent	10-19	20-29	30-39	40-49	50-59	60-69
63 Males	0	8	13	23	16	3
37 Females	1	6	7	16	7	0
100 Total	1	14	20	39	23	3

values of serum uric acid concentration. It is seen that the distribution of values among the males and the females is very similar, in each case at a maximum between 40 and 49 mg per cent. The mean serum uric acid content among the males was 4.4 ± 0.09 , among the females 4.0 ± 0.11 , and among the entire 100 non-gouty individuals 4.2 ± 0.07 mg per cent, respectively.

Included in the data of table 5 are values from two patients who had passed uric acid vesical calculi, but without evidence of gout. The serum uric acid content in one case was 4.5 mg per cent, and in the other case was 3.6 mg per cent.

The Serum Uric Acid in Non-Gouty Arthritis Twenty cases of non-gouty joint disease are included in the cases described above. The diagnosis in most of the 20 cases was arrived at only after exhaustive study. The serum uric acid values found in these cases are presented in table 6. It

TABLE VI
The Serum Uric Acid in Non-Gouty Arthritis

Diagnosis	Case Number	Serum Uric Acid, mg per cent
Rheumatoid Arthritis	1	2.4
" "	2	2.6
" "	3	2.9
" "	4	3.2
" "	5	3.3
" "	6	3.3
" "	7	3.5
" "	8	3.7
" "	9	4.3
" "	10	5.0
" "	11	5.6
" "	12	5.7
" "	13	5.9
" "	14	6.7
Hypertrophic Arthritis	15	4.2
" "	16	4.7
" "	17	4.9
Gonorrheal Arthritis	18	5.2
Multiple Foci of Osteomyelitis	19	6.2
Arthritis or Periostitis, cause unknown	20	6.7

is to be noted that the only cases among all of the non-gouty individuals in whom serum uric acid values in excess of 6.0 mg per cent were found include three listed in table 6 (cases 14, 19, and 20). All were males, none showed any clinical evidence of gout, and in none was there evidence of impaired renal function or of hepatic disease. Case 14 suffered from spondylitis deformans (rheumatoid arthritis), case 19 was one of multiple foci of osteomyelitis, and case 20 was diagnosed arthritis or periostitis, cause unknown.

Similar *infrequent* instances of elevated blood uric acid values in chronic, non-gouty arthritis have been reported by Pratt.¹⁵

The mean serum uric acid among the 20 cases of non-gouty arthritis was 4.6 ± 0.20 mg per cent. This value exceeds the mean of the entire 100 non-gouty individuals by only 0.4 ± 0.21 mg per cent, a difference of no statistical significance.

THE SERUM URIC ACID IN GOUT

Material The material of the present study consisted of 21 cases of gout. In nine cases the characteristic sodium urate crystals yielding a positive murexide test were obtained from tophi. In the remaining 12 cases



demonstrable or accessible tophi were not present. In these cases the diagnosis was based upon a characteristic history and physical finding, and was agreed upon by several observers. Both clinical and metabolic descriptions of cases 1 and 3 have been previously published⁵, case 2 forms the subject of a contemporary study¹⁶. Data on case 11 were reported in 1926 by Folin, Berglund, and Derick⁹.

In table 7 are presented all relevant data concerning the gouty subjects. All were males, with the exception of case 3. The ages of the patients ranged between 21 and 73 years. The duration of the disease varied from 4 months to 36 years. In ten cases chronicity of the disease was evidenced by deformities of joints or by characteristic roentgenologic bony lesions. In only seven patients was chronic gouty arthritis present (cases 1, 2, 3, 4, 11, 17, and 18). In the remaining 14 cases recurrent attacks of acute gouty arthritis had left no joint defects. All types of severity of gout were represented by these cases, ranging from case 2, of chronic gouty arthritis with multiple extensive ankyloses, and with superimposed attacks of acute gouty arthritis at intervals of a few weeks, to case 14, free of chronic changes and free of gouty attacks since the initial one three years previously.

In six cases there was present some degree of renal insufficiency, which by itself partially invalidates the diagnostic significance of the elevated uric acid values. The evidence for renal insufficiency was furnished principally by the non-protein nitrogen content of the blood and by the excretion of intravenously injected phenolsulphonephthalein, and in some cases by the urinary specific gravity during a concentration test. The values of non-protein nitrogen content in table 7 are to be interpreted in terms of the normal range of 20 to 35 mg per cent in whole blood, and of 20 to 30 mg per cent in serum. The excretion of phenolsulphonephthalein 15 minutes after the intravenous injection of 6 milligrams of the dye amounts to at least 25 per cent in normal individuals¹⁷. On the basis of these tests case 3 was considered one of moderate renal insufficiency, while cases 2, 11, 16, 17, and 18 represented minimal degrees of renal impairment.

Disease of the liver occurred in only one instance, case 17, in which acute yellow atrophy was present, accompanied by marked disturbance of hepatic function.

Among the 21 cases of gout the serum uric acid was determined on a total of 177 occasions, under various conditions to be described in detail below. On 174 occasions (98 per cent of total) the serum uric acid content exceeded 6.0 mg per cent, on 167 occasions (94 per cent of total) the value exceeded 7.0 mg per cent. Four values ranged between 14.1 and 14.8 mg per cent.

The Influence of a Purine-Free Diet Upon the Serum Uric Acid Level
That the consumption of a purine-free diet over a prolonged period is often followed by a slight depression of the blood uric acid level in gouty individuals has been reported by many investigators. The present data are

necessarily limited by the fact that the few subjects who consumed a purine-free diet did so for *relatively short periods*. Thus the longest such period, during which the serum uric acid was determined frequently, was three months (case 1). Moreover, there are lacking for comparison sufficient data on the same subject obtained while on a mixed diet. All of the data are depicted in table 7 in relation to other possible influences on the serum uric acid level. In no single case were there gathered sufficient values to permit a statistical comparison of the effect of variation only in the diet with all other influences equal. The few individual values of serum uric acid content while a purine-free diet was consumed *appear* to be slightly lower than those obtained while the subjects consumed a mixed diet (cases 1 and 3). On the other hand, it is evident that a purine-free diet, consumed over short periods, did not result in a fall of the serum uric acid content to a non-gouty level. Thus, of a total of 61 determinations among five patients (cases 2, 3, 4, and 8), free of acute gout and maintained on a purine-free diet without specific medication, only one value was as low as 6.0 mg per cent, while 55 values exceeded 7.0 mg per cent. Under similar restrictions of diet and of medication 51 values were obtained among six patients during attacks of acute gout. None of these values fell below 7.0 mg per cent.

The Influence of Various Drugs Upon the Serum Uric Acid Level In many instances the serum uric acid was determined while the patients were under the influence of one or more of several drugs which have been found, by many observers, to often lower the blood uric acid level. These drugs are aspirin, colchicin, and salyrgan. None of the subjects of the present study were under the influence of cinchophen or of related materials.

It may be seen in table 7 that only scanty data were obtained in any one patient while medication was administered, and *while a purine-free diet was consumed*, either during an interval between attacks of acute gout or during an attack. In case 1 on a purine-free diet and during several gouty attacks a total of 29 determinations of serum uric acid were performed while drugs were withheld, the mean of these values was 10.7 ± 0.17 mg per cent. While drugs were administered (aspirin, as much as 4 grams daily for several days, or colchicin, as much as 8 milligrams on any one day) 8 determinations of serum uric acid yielded a mean of 10.4 ± 0.38 mg per cent.

In a few instances drugs were apparently responsible for significant changes in the serum uric acid content. On one occasion the administration to case 1 of 3.0 milligrams of colchicin was followed by an apparent temporary fall of the uric acid to 8.5 mg per cent (depicted in figure 1, February 6, 1934), which succeeded a marked urinary excretion, on February 5, of 1.42 grams of uric acid. It is, of course, possible that this temporary fall was a result of some influence other than the colchicin. One of the lowest serum uric acid values among the entire 177 values was found in case 9 (table 7). During the nine days prior to the first determination (October

1, 1935) the left olecranon bursa was involved in an acute attack of gouty arthritis, by October 1 the active pain was absent, but pain on motion and moderate swelling and tenderness of the elbow were still present. During the previous five days the patient had consumed 26 grams of aspirin daily. The serum uric acid on October 1 was 5.7 mg per cent. Medication was withheld. The following day the serum uric acid was 8.2 mg per cent. That this low value of 5.7 mg per cent was related to the administration of the aspirin rather than to other influences is rendered likely by further data to be presented below.

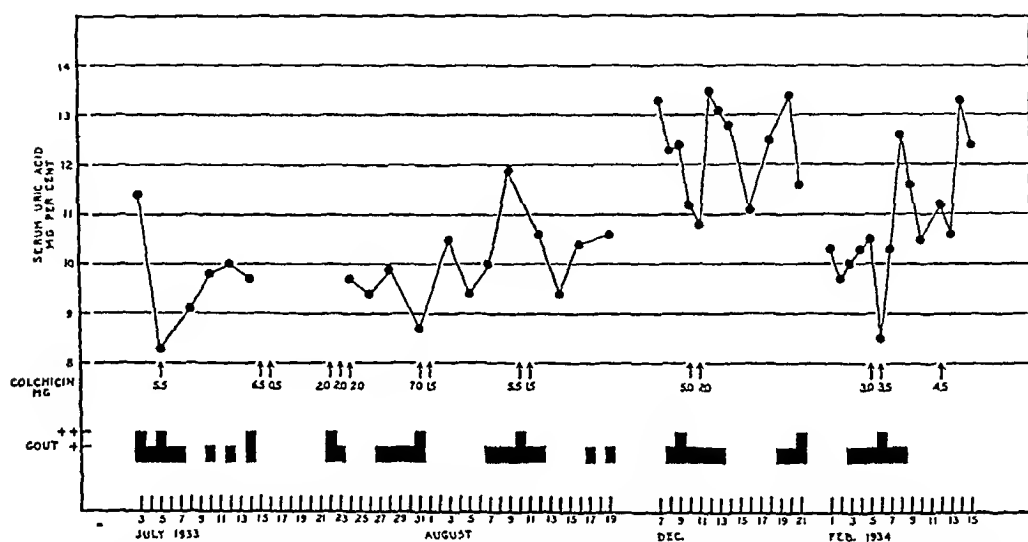


FIG 1 Case 1 Serum uric acid levels in relation to acute attacks of gout and to administration of colchicine (Purine-free diet, constant fluid intake of 2000 c c daily)

In four experiments among three patients the intravenous administration of salyrgan was followed by a significant temporary fall of the serum uric acid. Two of these experiments are depicted in figure 2, and a third in figure 3. In the latter instance the serum uric acid fell to 5.2 mg per cent, the lowest value among the entire 177 determinations. In a fourth experiment on case 1 a serum uric acid level of 11.9 mg per cent was succeeded, on the day after the intravenous injection of 2 c c of salyrgan, by a value of 8.1 mg per cent. In all of the above experiments the lowering of the serum uric acid levels followed a markedly increased urinary excretion of uric acid.

The Relationship of the Serum Uric Acid Level to the Attack of Acute Gouty Arthritis The possible relationship of the blood uric acid level to the attack of acute gouty arthritis has been studied by many observers, with almost as many divergent results as a consequence. That the blood uric acid rises just before an attack is a view shared by Lichtwitz and Stemitz,¹⁸ Lucke,¹⁹ and by Chrometzka.²⁰ That no such pre-attack rise occurs was stated by Gudzent.²¹ Pratt,¹⁵ writing in 1921, thought that the blood during

an acute attack usually contains slightly more uric acid than at other times Rathery and Violle²² and Thannhauser¹⁰ held that the uric acid falls during an attack Finally, Richter²³ maintained that the blood uric acid at the beginning of an attack is *either* elevated or depressed

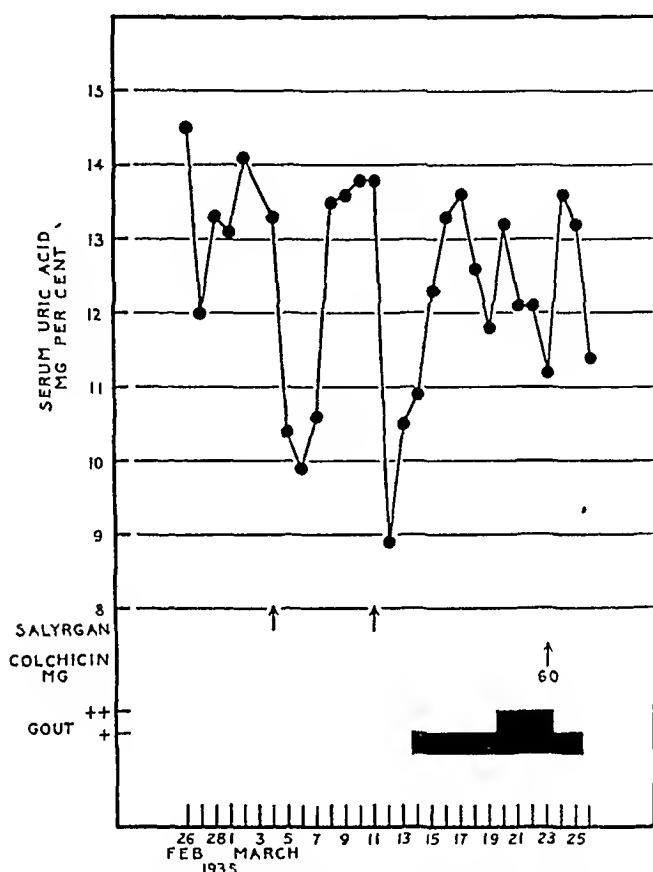


FIG 2 Case 2 Serum uric acid levels in relation to administration of salyrgan and to acute attack of gout (Purine-free diet, constant fluid intake of 2000 c c daily) On each day denoted by an arrow 1 c c of salyrgan was injected intravenously, after blood was drawn for analysis

In the opinion of the present writer, none of the above generalizations are based upon sufficient experimental evidence It is apparent that critical evidence must include very frequent observations of blood uric acid throughout an interval between acute attacks and during the attack of acute gouty arthritis, under controlled conditions of diet and of medication The present data constitute only an approximation to this ideal In figure 2 are depicted frequent observations of the serum uric acid in case 2 over a period of 29 days It is evident that prior to the administration of salyrgan on March 4, during an asymptomatic interval, the serum uric acid *fluctuated* considerably, and that similar *fluctuation* took place during the twelve days of the attack of acute gout (Any possible change of the uric acid level

just prior to the attack was, of course, masked by the effect of the salyrgan administered on March 11) Quantitatively much less marked variations were found in case 3, depicted in figure 4 These observations have been

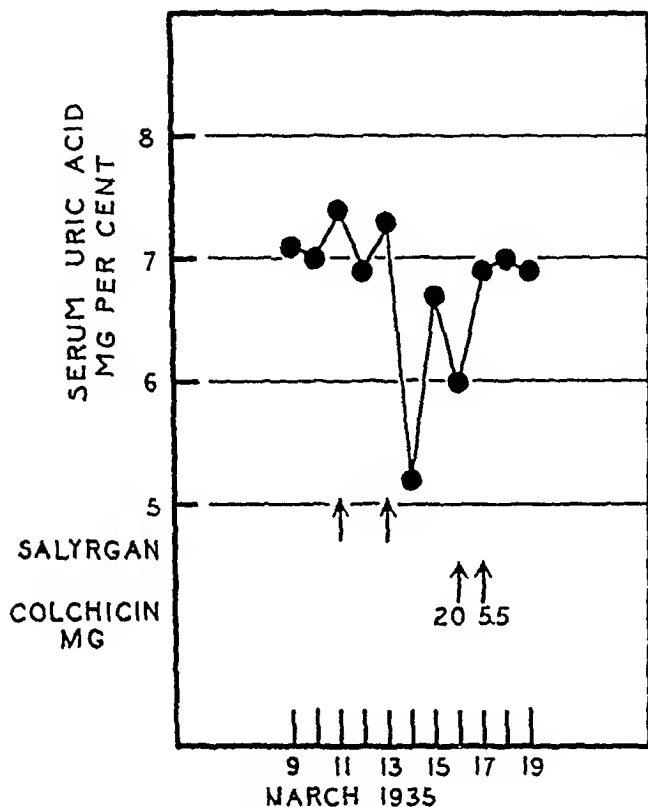


FIG 3 Case 4 Serum uric acid levels in relation to administration of colchicin and salyrgan (Purine-free diet, constant fluid intake of 2000 cc daily) On each day denoted by an arrow 1 cc of salyrgan was injected intravenously after blood was drawn for analysis

included in a previous report⁵ It is evident that the slight fall in the serum uric acid between April 6 and 10 might have been due to the change from a mixed diet to a purine-free diet on April 6, rather than related to the first attack of acute gout During the following asymptomatic interval prior to the second attack of acute gouty arthritis the serum uric acid *apparently* declined, and then *apparently* rose during the first two days of the attack More extended observations were made in case 1 and are presented in figure 1 (The data of December 7 to 21 have been included in a previous study⁵) In this case it is evident that the serum uric acid values, other than those possibly related to the administration of colchicin, showed a high degree of fluctuation and bore no consistent relation to the acute attacks Any apparent change just prior to or during the attacks was matched by equally apparent changes during the asymptomatic intervals

It seems to the writer that the data described above illustrate the futility

of seeking evidence of a change among the highly variable successive serum uric acid values by mere *inspection* of the uric acid curves. It was on the basis of such observations that the several different generalizations in the

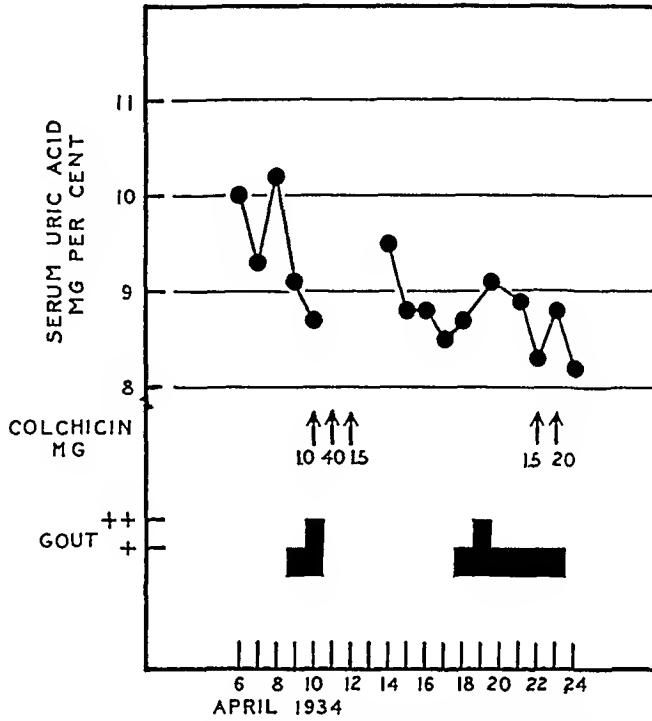


FIG 4 Case 3 Serum uric acid levels in relation to acute attacks of gout (Purine-free diet, constant fluid intake of 2000 c c daily)

literature were founded. Rather, the inherent variability of serum uric acid values requires the statistical treatment of a large number of such values. In two gouty subjects sufficient data were collected to justify a statistical analysis. All of the data on case 2, obtained while the patient consumed a purine-free diet and while medication was withheld, are included in table 7. It is seen that the mean of a total of 20 serum uric acid values collected during all parts of asymptomatic intervals was 12.4 ± 0.20 mg per cent, while the mean of 13 values measured during all parts of acute attacks of gouty arthritis was 12.1 ± 0.31 mg per cent. Similar but more extended observations were made in case 1. In table 7 are presented all of the serum uric acid values obtained while the patient consumed a purine-free diet without medication, in relation to 18 attacks of acute gouty arthritis over a period of one year.

It is seen that the mean of 25 serum uric acid values during asymptomatic intervals was 11.0 ± 0.18 mg per cent, while a practically identical mean of 10.7 ± 0.17 mg per cent was found among 29 determinations during acute attacks. Thus, when all phases of asymptomatic intervals were compared with all phases of acute attacks of gout in these two cases, no change

of the serum uric acid was observed. On the other hand, a more detailed analysis of the data in case 1 yielded a different interpretation. In table 8 are presented the serum uric acid values in relation to finer sub-divisions of

TABLE VIII
Serum Uric Acid Levels in Several Phases of Acute Attacks of Gouty Arthritis
Case 1 Purine-free diet, no medication

	Intervals		Acute Attacks of Gouty Arthritis	
	Earlier than 3 Days Preceding Attacks	Within 3 Days Preceding Attacks	First 2 Days	Subsequent to First 2 Days
Number of determinations	12	13	12	17
Range, serum uric acid, mg per cent	10.5-13.3	9.1-13.7	9.7-13.4	8.3-13.5
Mean, serum uric acid, mg per cent	11.7 \pm 0.18	10.3 \pm 0.25	10.6 \pm 0.22	10.8 \pm 0.24

the intervals and of the periods of acute gouty arthritis. It is evident that *during the three days prior to the acute attacks the serum uric acid fell* from a previous mean of 11.7 ± 0.18 mg per cent to one of 10.3 ± 0.25 mg per cent, a significant difference of 1.4 ± 0.31 mg per cent. The additional data of table 8 demonstrate that *during the gouty attack the serum uric acid remained unchanged*.

The Serum Uric Acid Level in Relation to the Severity of Gout. In only four of the present 21 cases of gout were there obtained a sufficiently large number of serum uric acid values, under comparable conditions of diet and of medication, to justify an attempt to correlate the height of the uric acid level with the severity of the disease. On the basis of frequency and severity of attacks, and the extent of chronic joint deformities, it was considered by several observers that the four cases, in the order of their severity, were cases 2, 1, 3, and 4. In table 7 it is seen that during asymptomatic intervals (purine-free diet, no medication) the means of the serum uric acid values of these cases were 12.4 ± 0.20 , 11.0 ± 0.18 , 8.6 , and 6.9 ± 0.08 mg per cent, respectively. During attacks of acute gouty arthritis (purine-free diet, no medication) the means were 12.1 ± 0.31 , 10.7 ± 0.17 , and 8.8 ± 0.06 mg per cent, respectively. (Data are lacking in case 4 in this category.) These respective differences in mean values are statistically significant. These data suggest, therefore, that in these four cases a more severe degree of gout was accompanied by a higher level of the serum uric acid.

Among the remaining 17 cases the serum uric acid values were insufficient in number to adequately characterize the uric acid level of any one case. However, the heights of the individual serum uric acid values did not appear related to such clinical aspects as the presence or absence of

chronic gouty arthritis or of tophi, the duration of the disease, or the frequency of attacks of acute gouty arthritis. With the exception of one of two values in case 9 (*vide supra*), the serum uric acid in every gouty individual was elevated.

The Serum Uric Acid Level Among Close Relatives of Gouty Individuals As early as 1916 Folin and Denis²¹ reported "a normal man of a gouty family" with an elevated whole blood uric acid (40 mg per cent). As far as the present writer is aware, similar additional studies have not been published in the vast literature concerning gout and uric acid in the blood. Although a systematic investigation of the uric acid metabolism of close relatives of gouty individuals has not been carried out, the following observations require mention. The serum uric acid was determined in three individuals, all adult males and completely free of a history or physical signs of joint disease. In all the non-protein nitrogen content of the blood was normal. The following serum uric acid values were found: a son of case 4, 67 mg per cent,* a son of case 6, 77 mg per cent, and a brother of case 5, 84 mg per cent, respectively.

The Significance of the Serum Uric Acid Level in the Diagnosis of Gout It is evident from the foregoing presentation that in only a few instances among the 177 determinations of the serum uric acid in 21 cases of gout, under various conditions, were the values within the range established in the 100 non-gouty subjects. Thus in case 4 (see figure 3 and table 7), among 14 determinations performed over a period of one month, one value of 52 mg per cent followed the administration of salyrgan on the previous day, three other values, unrelated to medication, were 60, 66, and 67 mg per cent, respectively, while the remaining 10 values ranged between 69 and 74 mg per cent. In case 9 the value of 57 mg per cent was found at the end of a five-day period in which 26 grams of aspirin were consumed daily, a second determination yielded a value of 82 mg per cent. Of the total 177 values, therefore, 175 values ranged between 60 and 148 mg per cent. In contrast, 97 of 100 determinations among 100 non-gouty individuals yielded serum uric acid values less than 60 mg per cent, three of the 100 values ranged between 60 and 67 mg per cent.

The high serum uric acid values found in three relatives of gouty individuals have been described above. This finding must obviously be brought to bear upon the interpretation of an elevated uric acid level in the absence of gout, renal insufficiency, disease of the liver, or leukemia.

Comparable with the present serum uric acid values in gout are the plasma uric acid levels ranging between 65 and 107 mg per cent, found in 11 determinations among nine gouty individuals by Folin, Berglund, and Derick.⁹

As far as the author is aware, the only other series of determinations, among gouty individuals, approaching the high proportion of elevated uric acid values of the present study is that of Jordan and Gaston²⁵. These

* This individual was studied in collaboration with Dr. John H. Talbott.

workers used the Folin 1930 method on unlaked whole blood. The upper limit of normal they took as 4.0 mg per cent. In 53 determinations among 17 cases of gout the whole blood uric acid exceeded 4.0 mg per cent in 47 instances.

The modern literature concerning the blood uric acid in gout, on the basis of older analytical methods, ranges between the view expressed by Thannhauser¹⁰ that an elevated value is a constant finding in gout, to the observations by Gudzent²⁶ of *normal whole blood uric acid values in one-third* of 26 cases of gout. Similar to the latter findings were the observations reported in 1928 by Hench, Vanzant, and Nomland²⁷. Among 100 cases of gout these authors found *normal whole blood uric acid levels in 28 cases*. Writing as late as 1936 Hench²⁸ found that *the whole blood uric acid was constantly elevated only in untreated chronic gouty arthritis*.

As far as the writer is aware, the present 177 determinations of the serum uric acid among 21 cases of gout, representing all types of the disease, under a variety of conditions, constitute the most extensive study of the problem of uricemia in gout. The results of this work amply confirm the original observations by Pratt² in 1913, based upon the use of the forerunner of modern colorimetric analytical methods, that hyperuricemia is practically constant in untreated gout. With the present method of estimation hyperuricemia is defined as a serum uric acid content in excess of 6.0 mg per cent.

SUMMARY

The determination of uric acid in blood by means of the Folin 1933 method yielded experimental evidence for the view that analysis of *serum*, derived from blood allowed to clot under oil, furnishes more valid data than does *whole blood*.

The fasting uric acid in 100 non-gouty individuals consuming a mixed diet ranged from 1.9 to 6.7 mg per cent, with a mean of 4.2 ± 0.07 mg per cent. In 97 individuals the serum uric acid was less than 6.0 mg per cent.

The serum uric acid was determined on 177 occasions in 21 cases of gout, under various conditions. The serum uric acid values ranged from 5.2 to 14.8 mg per cent. On 174 occasions (98 per cent of total) the value exceeded 6.0 mg per cent, on 167 occasions (94 per cent of total) the value exceeded 7.0 mg per cent.

The consumption by gouty individuals of a purine-free diet during periods shorter than three months did not significantly influence the serum uric acid level. The administration of aspirin, colchicin, and salyrgan to gouty individuals on several occasions was followed by an apparent temporary fall of the serum uric acid level.

The serum uric acid frequently determined in four gouty individuals, apparently exhibited marked fluctuation both during asymptomatic intervals and during attacks of acute gouty arthritis. An intensive study of one case

of gout over a period of one year demonstrated a significant fall of the mean serum uric acid level during a three-day period preceding attacks of acute gouty arthritis, during the attacks the serum uric acid level remained unchanged

Among four cases of gout an apparent direct correlation was found between the height of the serum uric acid level and the severity of the disease

The serum uric acid was determined in the son of each of two gouty individuals, and in the brother of a third gouty individual. These relatives themselves were free of gout. Their serum uric acid concentrations were 6.7, 7.7, and 8.4 mg per cent, respectively

The author is indebted to Drs. Walter Bauer, Arlie V. Bock, and Saul Hertz of this clinic for permitting observations on patients from their private practice. Dr. Walter Bauer, and Dr. Harry C. Trimble of the Department of Biological Chemistry, Harvard Medical School, have made many helpful suggestions during the course of the work and in the preparation of the manuscript.

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“PLATE-LIKE” ATELECTASIS OF THE LUNG *

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THE clinical importance of atelectatic conditions of the lung and their proper roentgenological recognition has recently been emphasized. Attention has been called to the frequent occurrence of atelectasis in tuberculosis,¹ in bronchiectasis,^{2, 3, 4} in minor upper respiratory infections.⁵ Usually the collapse of a whole lobe or nearly a whole lobe has been described. The so-called basal triangular shadow as evidence of lower lobe collapse, the triangular shadow at the apex in atelectasis of the upper lobe, as well as the appearance of the collapsed middle lobe have been described in detail by numerous writers.^{6, 7, 8, 9, 10} In addition to the characteristic form of the dense shadow cast by the collapsed lobe, the presence of a mediastinal shift is generally considered to be a valuable sign in the differential diagnosis of atelectasis.¹¹ In partial collapse, the mediastinal shift may be completely absent, but the displacement of the interlobar septum towards the diseased lobe is helpful in making a diagnosis.^{10, 12} The smallest localized areas of atelectasis which occur, due to obstruction of a bronchus of the second or third division, do not, however, produce any shift of the interlobar septum. The term generally used to describe small atelectatic areas is that of “patchy atelectasis.” Patchy atelectasis is supposed to be indistinguishable from bronchopneumonic infiltration.¹³

Recently, Fleischner¹² has convincingly shown that small areas of pure atelectasis without complicating secondary changes of the parenchyma, are represented by “plate-like” shadows in the lung, which appear as horizontal stripes in both postero-anterior and lateral views. Previously, such horizontal stripes frequently have been mistaken for fibrinous deposits on the pleura.¹⁴ Fleischner observed these stripes associated with three groups of conditions

1 Abdominal diseases

In this first group of diseases the horizontal shadow stripes had been observed by other authors previously to Fleischner,^{14, 15, 16} and had been interpreted as being due to pleurisy.

2 After contusions of the chest

3 Associated with minor upper respiratory infections

Fleischner, by autopsy controls, demonstrated that these plate-like shadows were due to small atelectatic areas. It seemed to us that a further

* Received for publication August 16, 1937

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proof could be offered by observing the development of these shadows during the reexpansion of a lobar infectious atelectasis. In infectious atelectasis a previously normal lobe collapses and often reexpands before severe

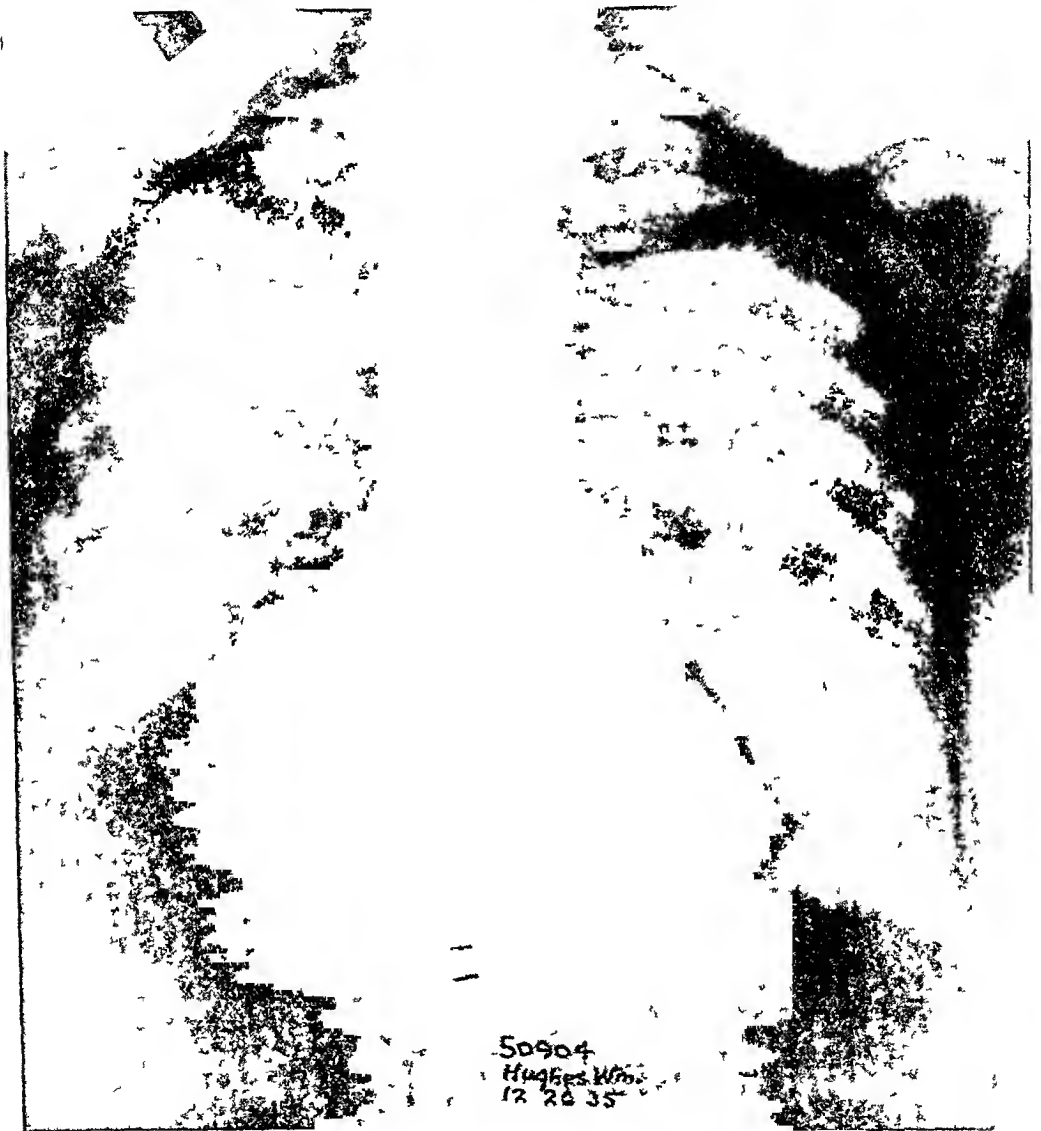


FIG 1 P A view Dec 24, 1935 Triangular shadow at the base of the right lung field merging with the shadow of the heart and the right diaphragm Typical appearance of collapse of the right lower lobe

chronic changes, such as bronchiectasis or fibrosis, develop^{5 17} It has been shown that the collapse in these cases is not to be explained by a gross plugging of a main bronchus, but by the presence of tenacious sputum in numerous smaller sized bronchi. During the stage of reexpansion, a few smaller-sized bronchi may remain plugged longer than others. The small atelectatic pulmonary areas supplied by these bronchi should be demon-

strable at this stage as horizontal shadow stripes. We have seen that this occurs. In a number of cases of typical acute lobar collapse in children due to upper respiratory infection, the horizontal shadow stripes appeared on the



FIG 1a Lateral view Dec 24, 1935 Note collapsed right lower lobe as a dense shadow overlying the spine

roentgen-ray film during the stage of re-inflation. They represented at this time the only abnormal finding. Clinically, the health of the patient seemed to be fully restored. The following case may be reported as an example.

CASE REPORT

Case 1 (I am indebted to the Boston Floating Hospital for the case history.) W. H., a nine year old boy, was admitted to the Boston Floating Hospital on

December 23, 1935, because of fever and anorexia of 10 days' duration. He had suffered from measles at the age of six, and whooping cough at four. Since the whooping cough the boy had frequent attacks of cough and fever during the winter.

On admission, there was rapid breathing and cough. The examination showed



FIG 2 P A view Oct 5, 1936 Collapse of the right and the left lower lobes

limitation of expansion on the right side and dullness posteriorly from apex to base. The breath sounds were diminished and expiration prolonged over this area. The temperature was 101° on admission and terminated by crisis one day later. It stayed normal thereafter.

Films taken one day after admission showed a typical triangular shadow at the right base indicating total collapse of the right lower lobe. There was also some mottling in the left lower lung field behind the heart (figures 1 and 1a).

The patient gradually improved and was discharged on January 16, 1936, to

a recreation home. Roentgen-ray examinations were not repeated at the time of discharge. It was intended to introduce lipiodol into the right lower lobe at a later date, to determine whether or not bronchiectases were present. This seemed advisable because of the present conception that bronchiectasis may develop in cases of spontaneous lobar atelectasis^{18, 4, 7, 5}

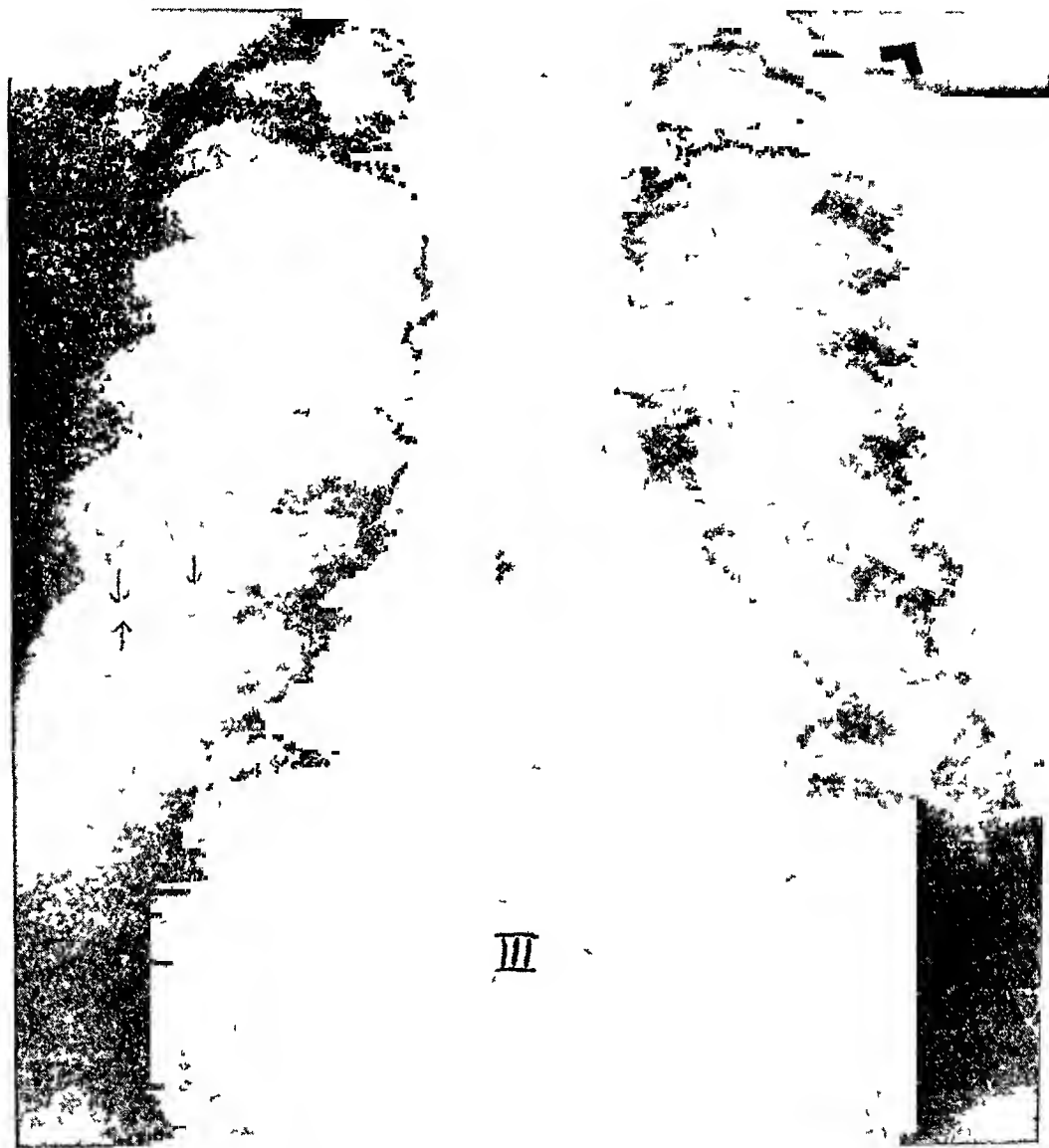


FIG 3 P A view Nov 2, 1936. The right lower lobe has partially reexpanded. Indefinite cloudiness in the right cardio-diaphragmatic angle. Arrows indicate the displaced interlobar septum.

In March 1936, three months later, chest films were again taken and showed the right lung to be entirely normal. The previously collapsed right lower lobe had completely reexpanded.

On September 27, 1936, nine months after the original episode, the patient was re-admitted to the Boston Floating Hospital because of fever, cough, shortness of

breath, and pain in the region of the right lower chest of one week's duration. In the interval between March and September, the boy had been well, with the exception of one week's sickness in June, with similar symptoms.

On admission the boy appeared acutely ill, dyspneic, coughing, raising a considerable amount of sputum. Physical findings showed impaired resonance at both bases,

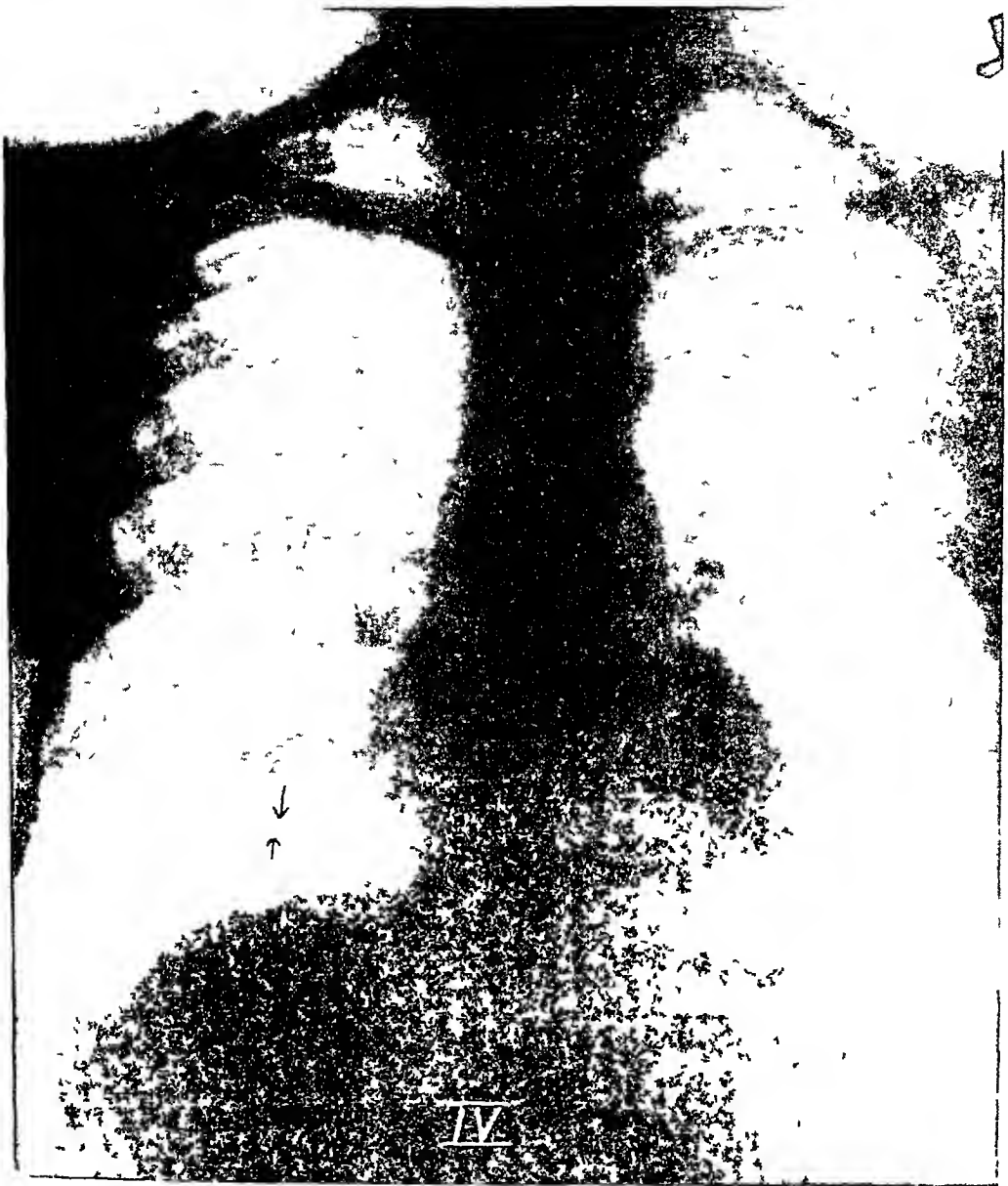


FIG 4 P A view Nov 30, 1936 Arrows indicate a horizontal shadow stripe in the right lower lobe, which represents "plate-like" atelectasis

with diminished breath sounds at the left base. No râles were heard. Tactile fremitus was slightly more pronounced on the right side. The temperature was 103° on admission and dropped to normal at the end of 12 days. Films taken one week after admission (October 5, 1936), while the patient was still acutely ill, showed

collapse of the right and left lower lobes (figure 2) Reexamination on November 2, 1936, showed marked improvement There was now partial collapse of the right lower lobe only (figure 3) Clinically, the child had markedly improved in the meantime The temperature was normal The cough had disappeared On November

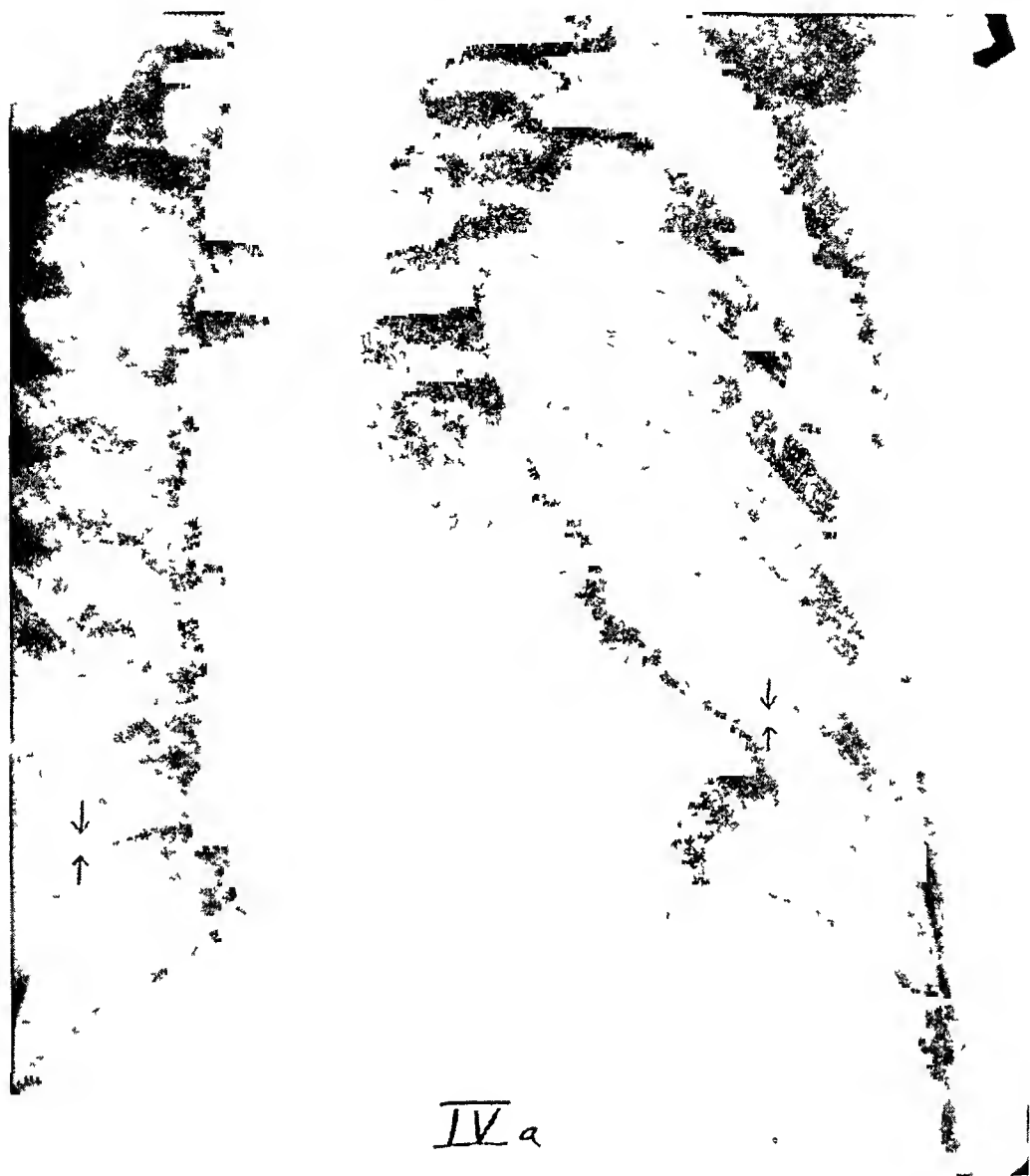


FIG 4a Right oblique view Nov 30, 1936 Arrows indicate the "plate-like" atelectases In this view an atelectatic area in the left lower lobe has become visible, which in the P A view was hidden behind the heart shadow

30, 1935, the child appeared clinically well Films taken at this time showed both diaphragms smooth in outline, freely movable with respiration There were two transverse shadow stripes in the right lower lung field and one in the left lower lung field

Interpretation These shadow stripes were considered to represent minute

atelectases due to occlusion of small-sized bronchi in the right and left lower lobes (figures 4 and 4a)

In differential diagnosis, pleural adhesions alone have to be considered. The appearance of the atelectatic areas as thin stripes in both the anterior and lateral films makes it obvious that we are dealing with a plate-like and not with a linear structure. The intrapulmonary origin is therefore evident.

Fleischner explains the appearance of these plate-like shadows by a mechanism which he calls "directed collapse." While in pneumothorax the lung can retract from the lateral chest wall due to the change of pressure within the chest cavity, the conditions for collapse in obstructive atelectasis are fundamentally different. Here, the lung cannot retract from the chest wall. Even if no pleural adhesions are present, the negative pressure acts as an adherent force between the surface of the lung and the chest wall and prevents the collapse of the lung toward the hilus. As there is no possibility for the lung to shrink in a costo-mediastinal direction as in pneumothorax, the tendency of the atelectatic area to diminish in extent can only take place in a crano-caudal direction, perpendicular to the axis of shrinkage in pneumothorax.

CONCLUSION

A case of acute lobar collapse due to upper respiratory infection is reported. In the end stage of reexpansion, thin horizontal shadow stripes were seen in the area previously collapsed, and were interpreted as "plate-like" minute areas of atelectases.

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A COMPARISON OF THE PRESSURES IN ARM VEINS AND FEMORAL VEINS WITH SPECIAL REFERENCE TO CHANGES DURING PREGNANCY

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KNOWLEDGE of the general level of venous pressure may be usefully applied to the evaluation of cardiac failure and of pericardial obstruction and it may sometimes serve as a guide to the management of these conditions. These applications are widely known and practised. This communication is concerned, not with the general level of venous pressure, but with the study and utilization of local venous pressures in the understanding and description of disease. My colleagues and I were led to make the observations here reported by certain phenomena encountered during our study of pregnant women¹. During the physical examination of such patients observation was made of an increase in the number and prominence of visible veins over the abdomen, suggesting the development of a collateral circulation. Assuming that collateral venous channels develop in relation to some obstruction to venous blood flow, we undertook a comparison of the pressures in two widely separated portions of the venous system. These were the femoral vein and a vein in the antecubital space. These two points are approximately the same distance from the heart, moreover, one is in the system of the inferior vena cava and distal to the apparent collateral circulation, while the other is in the system of the superior vena cava.

Measurements of venous pressure were made by the direct method described by Moritz and von Tabora². The patient lay on his back in bed and the zero point of the manometer was set at a level 5 cm. dorsal to the fifth costal cartilage. It was found advisable to precede the measurement by a period of rest and to minimize discomfort by the injection of a drop of local anesthetic.

Only some observations by Runge,³ who compared arm vein pressure with that in veins near the knee, and the study of 11 patients with diverse conditions by Ferris and Wilkins⁴ offer information bearing on this point. Therefore, the arm and leg venous pressures were studied in a group of non-pregnant individuals, including normal persons and those with con-

* Read in part at the meeting of the Association of American Physicians, Atlantic City, New Jersey, May 5, 1937.

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ditions already known to affect local or general venous pressure The results of these preliminary observations are summarized in table 1

TABLE I
Examples of Venous Pressure in Arm and Leg in Normals and in Patients
with Various Circulatory Disturbances

		Venous Pressure	
		Arm	Leg
		mm H ₂ O	mm H ₂ O
A	<i>Normal circulatory system</i> 1 Psychoneurosis	58	58
B	<i>Heart disease</i>		
1	<i>Without failure</i>		
	2 Hypertension (B P 210/110)	42	41
	(B P 212/140)	48	55
2	<i>With failure and without ascites</i>		
	3 Hypertension	182	178
3	<i>With failure and with ascites</i>		
	4 Aortic regurgitation and hypertension	238	269
4	<i>Pericardial obstruction</i>		
	5 Constrictive pericarditis	320	304
	6 Pericardial effusion	165	167
C	<i>Mediastinal tumor</i> 7 Lymphoma of superior mediastinum	360	60
D	<i>Abdominal tumors</i>		
	8 Fibromyoma of uterus before operation	104	274
	Fibromyoma of uterus after operation	66	55
E	<i>Ascites not due to heart disease</i>		
	9 Cirrhosis	105	146
	Cirrhosis after removal of 5,000 c c	88	88

In individuals without heart disease or local venous obstruction, the venous pressure is not elevated, and is nearly identical in arm and leg under the conditions of these observations. In patients with heart disease but without congestive failure or pericardial obstruction, the venous pressure is similar in arm and leg and is not elevated. In patients with manifest congestive failure and in those with pericardial obstruction from either fluid or constrictive scar the pressure is elevated. The pressure in such cases is identical (or nearly so) in arm and leg, unless there is a considerable accumulation of fluid in the abdomen. When ascites is present the leg pressure may be higher than the arm pressure. Removal of ascites in such cases results in similar pressures in arm and leg, at a level which is still above normal but often somewhat lower than the original arm pressure.

These impediments to venous flow are central, i.e. they are due to right ventricular failure or to pericardial obstruction and they interfere with the entry of blood into the heart. Obstruction may also be at some peripheral

point, in which case venous pressure may be elevated locally and may differ widely in arm and leg. Examples are given of a patient with a mediastinal tumor in whom the arm pressure is higher than that in the leg, and of patients with intra-abdominal tumor or noncardiac ascites in whom the leg pressure is higher than that in the arm. In some of these patients the collateral circulation led to the visible distention of superficial veins.

TABLE II
Pressure in the Veins in Arm and Leg of Women During and After Pregnancy

No	Months of Pregnancy	Venous Pressure		Time after Delivery	Venous Pressure	
		Arm	Leg		Arm	Leg
		mm	H ₂ O		mm	H ₂ O
1	3 months	58	78	6 months	65	70
2	3½ months	77	100			
	8½ months	56	240	Unknown	108	97
3	4 months	102	163	5 months	—	118
4	6½ months	85	154			
	7½ months	98	175			
5	7 months	156	208			
6	7 months	102	232			
7	7½ months	80	145			
8	8 months	110	201	5 months	—	102
9	8 months	78	161	4 months	108	92
10	8 months	102	236	10 days	108	72
11	8 months	76	200			
12	8 months	110	215			
13	8 months	90	170	6 months	30	30
14	8½ months	51	183	6 months	89	81
15	8½ months	145	181	7 days	91	87
16	8½ months	95	220	1 month	110	85
17	8½ months	138	190	6 weeks	118	97
18	8½ months	82	188	6 days	162	63
19	9 months	62	265			
20	"Near term"	55	178			
21	"At term"	78	198			
22	"At term"	82	210			
23				17 days	48	55

With these observations in mind we may proceed to a consideration of the venous pressures in the arm and leg of pregnant women. Table 2 and figure 1 record observations in 22 women and in every case the leg pressure during pregnancy is notably higher than that in the arm. It is seen that by the fourth month of pregnancy the rise takes place and that it persists and even increases throughout pregnancy. The pressure falls abruptly to normal with delivery.

Similar observations were then made in pregnant bitches. The jugular vein was utilized instead of one at the elbow. It was found that the pressures in the femoral veins of these pregnant animals were higher than those in the jugular veins, and that the difference was comparable to that observed between arm and leg veins in pregnant women. After delivery the dif-

ference was not present When the pregnant animal's abdomen was opened the femoral venous pressure did not alter, which led us to conclude that the

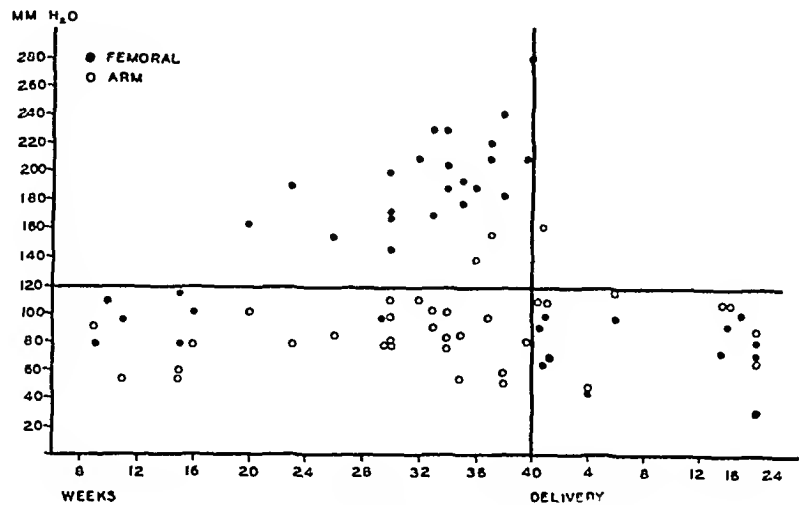


FIG 1 Venous pressure in pregnancy

elevated femoral venous pressure was not due to an increase in general intra-abdominal pressure

Further observations were made concerning the relation of general abdominal pressure and the pressures in the femoral and jugular veins by the injection of salt solution into the peritoneal cavity of dogs An example of these experiments is shown in table 3 Two points may be noted

TABLE III

Venous Pressure in Femoral and Jugular Veins in Relation to Elevated Abdominal Pressures in a Dog

C c Saline Injected in Peritoneal Cavity	Intra-Abdominal Pressure	Femoral Venous Pressure	Jugular Venous Pressure
	mm H ₂ O	mm H ₂ O	mm H ₂ O
0		-2	-4
300		+6	-3
800	+20	+37	-2
1400	+60	+72	±0
2000	+145	+148	-1
2600	270	270	-1
2800	345	342	+2
3000	410	410	+4
3200	490	495	+11
3300	525	525	+12
All fluid removed from abdomen		0	+8

Note The scales were set so that the zero point was at the level of the apex beat

1 The leg venous pressure does not rise until the general abdominal pressure begins to go up

2 When the leg venous pressure reaches a height comparable to that observed in pregnant women the abdominal wall is tense

Since the abdominal wall of pregnant women with a high femoral pressure is not tense it is evident that an increase in general abdominal pressure is not the mechanism leading to the elevated femoral pressure in pregnant women

These observations and those concerned with abdominal tumors suggest that an important factor in the high femoral pressure is the pressure of the gravid uterus upon the veins. This concept is borne out by the following observation in pregnant bitches. When the gravid uterus was lifted from its normal position in the abdomen and supported so that it did not press on the great veins the pressure in the femorals fell, although it still remained above the pressure in the jugulars

So much for venous obstruction. But the pressure in any vessel is influenced not only by the resistance to outflow but also by the amount and pressure of the blood flowing into it. This point may be illustrated by the situation existing in the veins adjacent to an arteriovenous fistula. In spite of the minimal resistance offered by normal veins the pressure in these vessels is markedly elevated, even some distance away from the fistula

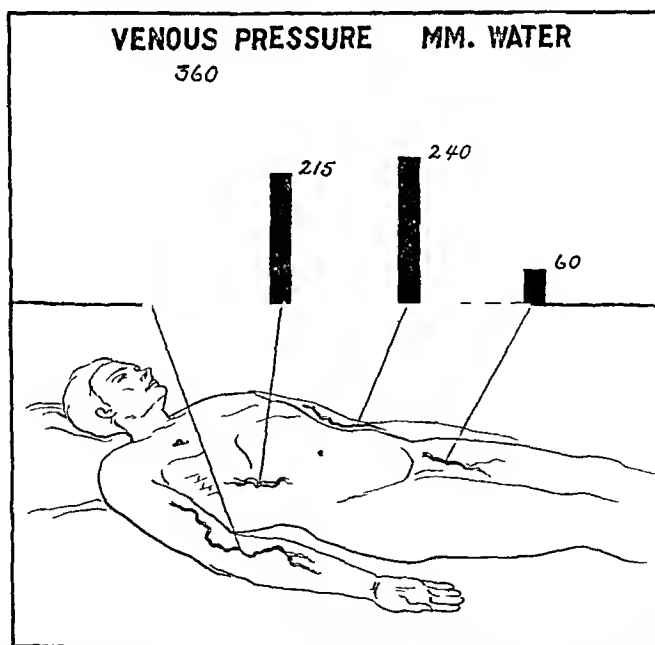


FIG 2 Venous pressures at various points in a patient with a neoplasm of the superior mediastinum

There exists evidence that a large volume of blood at a relatively high pressure enters the venous reservoir by way of the placenta. Indeed it may be shown that the maternal placental circulation constitutes a modified arteriovenous fistula. There appears no reason to doubt that the factor of increased inflow is an important cause of the elevated femoral pressure

The knowledge of venous pressures acquired by these observations may be utilized in the study of conditions other than pregnancy. Two examples may be cited.

The first is a woman of 45 who entered the hospital with a history of increasing dyspnea and abdominal enlargement. The general evidence of heart failure was acceptable until it was observed that even after removal of the ascites the femoral venous pressure was higher than the arm (180 mm as compared to 115 mm). This led to a search for an obstruction to venous flow, which was subsequently demonstrated to be an intra-abdominal neoplasm riding directly over the inferior vena cava and partially occluding it. There were no physical signs, other than the differential venous pressures, which pointed to a tumor in this location.

The second patient is a man whose venous pressures are indicated in figure 2.

The venous pressures at these different points, even in the presence in this case of an equivocal roentgen-ray, point clearly to an obstruction in the superior mediastinum. Further roentgen-ray examination verified this localization.

We conclude from these observations

1 Venous collaterals develop when there is a higher venous pressure in one area of the periphery than in another.

2 The high pressures in the femoral veins of pregnant women are brought about by at least two mechanisms

- (a) The inflow of a large amount of blood via the placenta
- (b) Obstruction to venous outflow by the gravid uterus

3 The comparison of venous pressures in different parts of the body is useful in the understanding and description of disease and may on occasion even be applied to its diagnosis.

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SPLENIC IRRADIATION IN THE TREATMENT OF PURPURA HEMORRHAGICA

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OUR experience with splenic irradiation in purpura hemorrhagica is not in agreement with that of Mettier,¹ who states, "Repeated roentgen irradiation over the spleen in suitable doses is an excellent means of increasing the number of circulating blood platelets in patients with idiopathic thrombocytopenic purpura hemorrhagica "

EARLY RESULTS

The term control of coagulation was used loosely, and still is, by some to include control of bleeding of any type without attempting to isolate that occurring in purpura hemorrhagica. Therefore, many data reported in the literature can not be considered as significant. Costa Storico² states that as early as 1912 Triboulet, Weil, and Parof report favorably on the use of splenic irradiation in hemorrhage. Stephan,³ in 1920, noted the cessation of bleeding following its use and considered the spleen as the central organ of coagulation. He includes in his report the results of Bucky and Guggenheimer. Aubertin, Levy, and Lereboullet,⁴ using an irradiation of 200 R over the spleen, reported the control of the bleeding time followed by a platelet increase in a patient with rheumatoid purpura. Schneider,⁵ in 1929, reported favorably on the use of this method, but the blood studies are not complete. In 1932 Hippe and Kochmann⁶ stated that excellent results in this disease were obtained by Klempere, Goia, and Bignoni and they conclude, "Through our experience we have reached the point not to lose any time with other treatment in the case of severe thrombopenic bleeding, but irradiate the spleen at once." In 1935 Mettier, Stone, and Purviance⁷ report on the use of irradiation in eight patients, stating that there was a cessation of bleeding and a prompt and satisfactory rise in platelets. Rudisill²¹ reports similar results in seven patients.

Pancoast, Pendergrass, and Fitz-Hugh,⁸ in 1925, report that Corey and Mandelstaum were unable to obtain an effect similar to those already described. Hippe and Kochmann⁶ state that Korger, Leschke, Wittkower,

*Read before the Section on Medicine, College of Physicians of Philadelphia

Received for publication September 16, 1937

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Prepared in part under the J. Ewing Mears Research Fund and in part through the generosity of Mr. Charles Groff, of Greenwich, Conn.

We are indebted to Miss Virginia Mitchell for collection of many data relating to this subject and to Mr. Eric Plehn for the translation of many articles in the bibliography and others not included.

Mandelstaum and Pakozdy completely declined the use of roentgen-ray for the treatment of thrombopemic purpura Thormann,⁹ in 1928, pointed out that Dolbe and Wertheim criticized the use of irradiation of the spleen in this disease and that Kleistadt had no success in treating essential thrombopemic purpura by this method, and that furthermore Passon felt that splenic

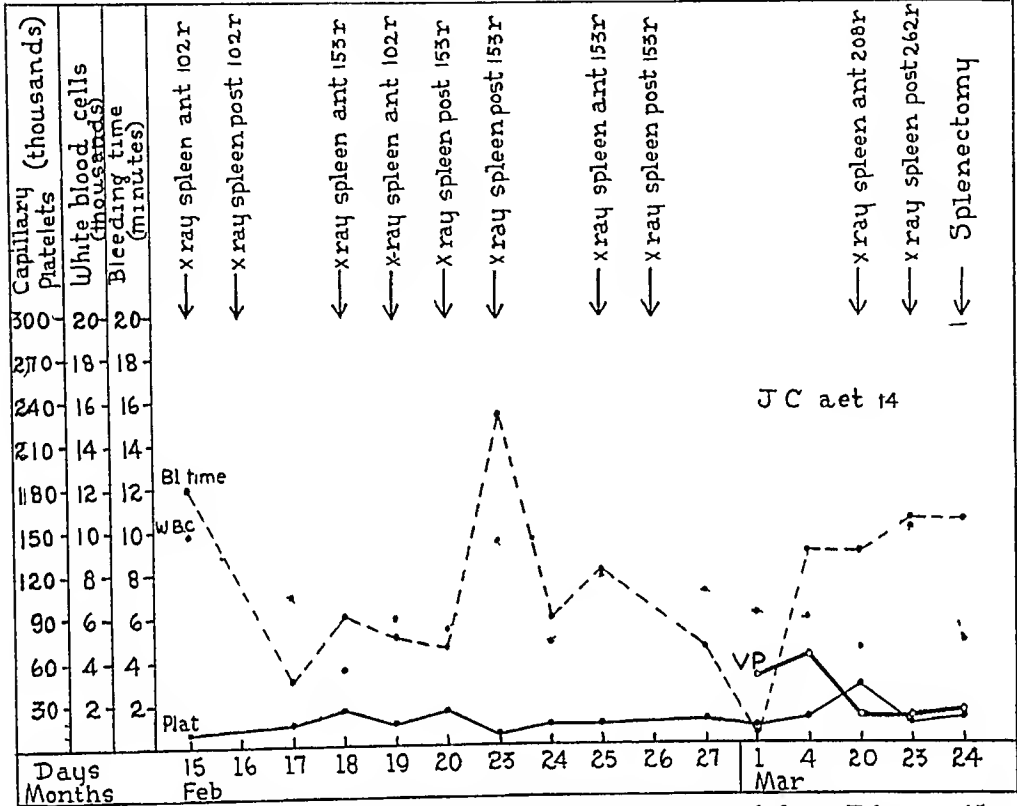


FIG 1 J C Adequate roentgen-ray to spleen administered from February 15 to March 23 No effect upon platelets or hemorrhagic phenomena Splenectomy March 24 Patient well in all respects August 11, 1937

irradiation should not be used in the case of children Schneider,⁵ in 1929, notes that Meda was entirely unsuccessful in treating this disease by this method Marzullo,¹⁰ in 1933, failed to find any significant clinical improvement in his patients after roentgen-ray therapy, and further states that the platelets did not rise above 100,000 Pancoast, Pendergrass and Fitz-Hugh report their results as inconclusive with this form of treatment, all cases coming to splenectomy

RATIONALE

Two functions of the spleen seem to be well established, (1) the reservoir function, and (2) the destruction of red cells, granulocytes and platelets by the clasmatocytes of endothelial origin in the spleen One wonders how the cells of the spleen are able to pick out the platelets and destroy them and not destroy the granulocytes and red cells at the same time We know,

however, that in malignant neutropenia the granulocytes are few in number and the platelets remain at a practically normal level. In hypoplastic anemia and aleukia hemorrhagica both platelets and granulocytes may be reduced to a very low level. This leads us to consider the condition of the bone marrow, in which we find the megakaryocytes normal in number in some purpuric patients and reduced in others. Probably the number of

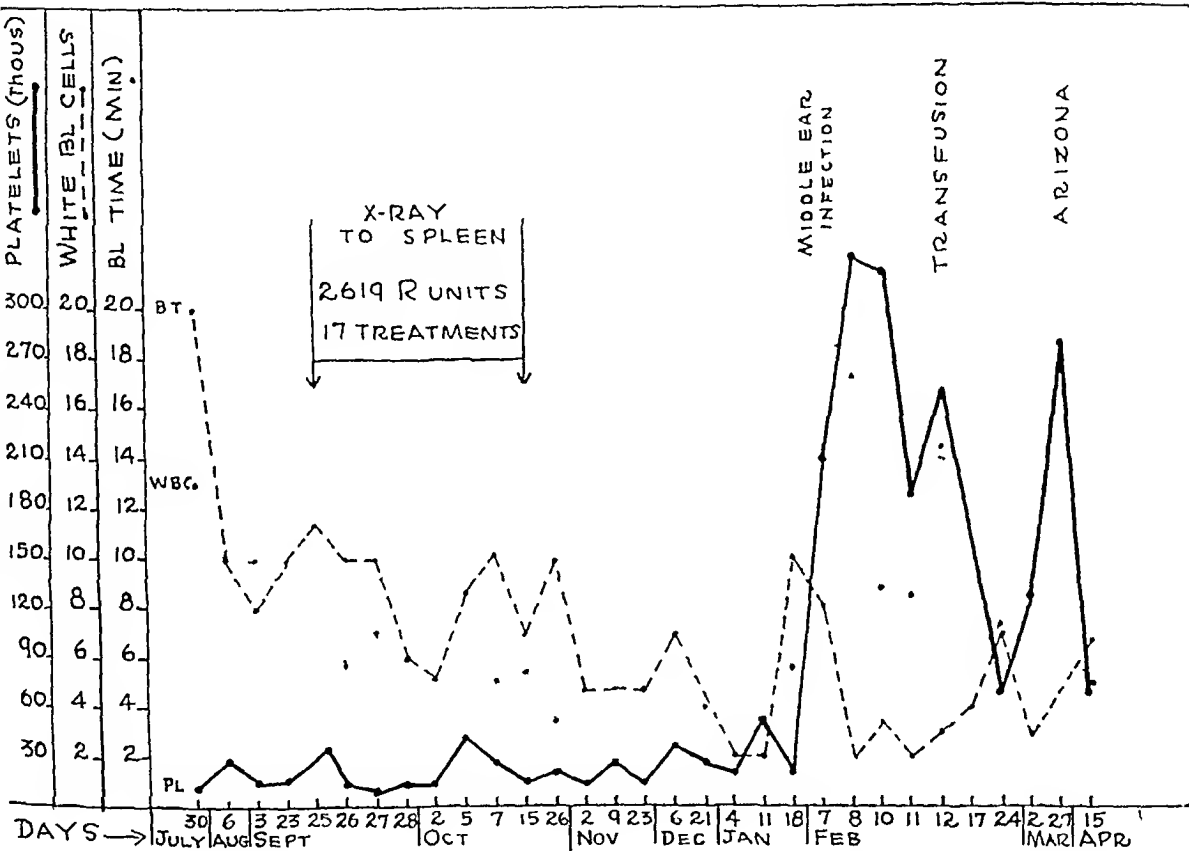


FIG 2 J P Chronic purpura with acute exacerbations. Roentgen-ray to spleen ineffective. January 1936 developed middle ear disease, mastoiditis, painful and swollen joints, erythema nodosum (purpura rheumatica). Following this the platelets rose to normal, bleeding time fell to normal. Platelets dropped to a low level a month later, rose again while patient was in Arizona. Menstrual cycle established, periods normal. Platelet level at present normal, no hemorrhagic phenomena.

megakaryocytes is not as important as the functional ability of the megakaryocytes that are present in the bone marrow at a given time. More study should be given to the condition of the megakaryocytes as well as to their actual number.

It seems unlikely that the platelet lack in purpura hemorrhagica can be explained purely on the basis of the collection of "hyaline" masses of platelets in thrombosed capillaries, as described by Baehr,¹¹ if roentgen-ray to the spleen is an effective form of treatment. It may be, however, that depressing or removing splenic function in some way permits some of these

platelets to get back into circulation Does the spleen have a depressing effect on platelet formation in the bone marrow? This seems unlikely and presumes the presence of a splenic hormone The importance of anoxemia in bone marrow erythrocytic development is well established and may play

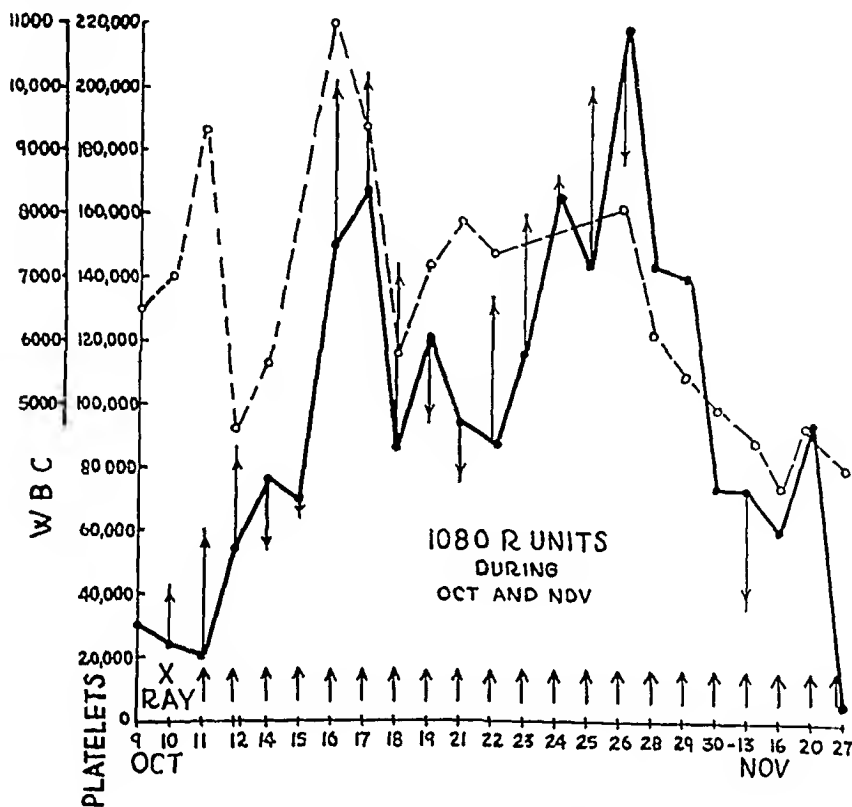


FIG 3 J G Chronic purpura Snake venom administered over a three month's period before roentgen-ray treatment to spleen Following this platelets rose to a high level after the fourth treatment and reached a peak after the fourteenth, then fell to 6,000 per cu mm on November 27 Roentgen-ray treatment discontinued because of the accompanying drop of white cells to 2,700 Additional treatment increases total R units to 1620

a significant part in megakaryocytic activity Schurer¹² discusses the wide usage of splenic irradiation in treatment of cases of "septic disease," noting favorable results The dosage is not mentioned, but he concludes that the good effect obtained is due to an outpouring of white blood cells as a result of lymphatic damage or as a result of an irritating effect on the reticulo-endothelial system, thereby increasing the function We see, therefore, that one group use roentgen-ray to depress the function of the clasmatoocytes and another to stimulate the reticulo-endothelial system, of which the splenic clasmatoocyte is a part Who is able to determine the dose of roentgen-ray to the spleen which may stimulate in one case and depress in another?

EXPERIMENTAL

Using $\frac{1}{4}$, $\frac{1}{2}$ and 1 erythema dose with filters of 1 Al, 0.3 Cu, 5 Al and 2 Al in rabbits and injecting 1 cc of iron oxide intravenously, Schus-

terowna¹³ concludes that the cells of the reticulo-endothelial system in the spleen were less able to absorb iron and, therefore, possess less phagocytic ability. Cosati,¹⁴ using 100 R to the exteriorized spleen at 13 cm with slight filtration, failed to find evidence of marked splenic destruction sufficient to endanger gross splenic function. From this work it would seem

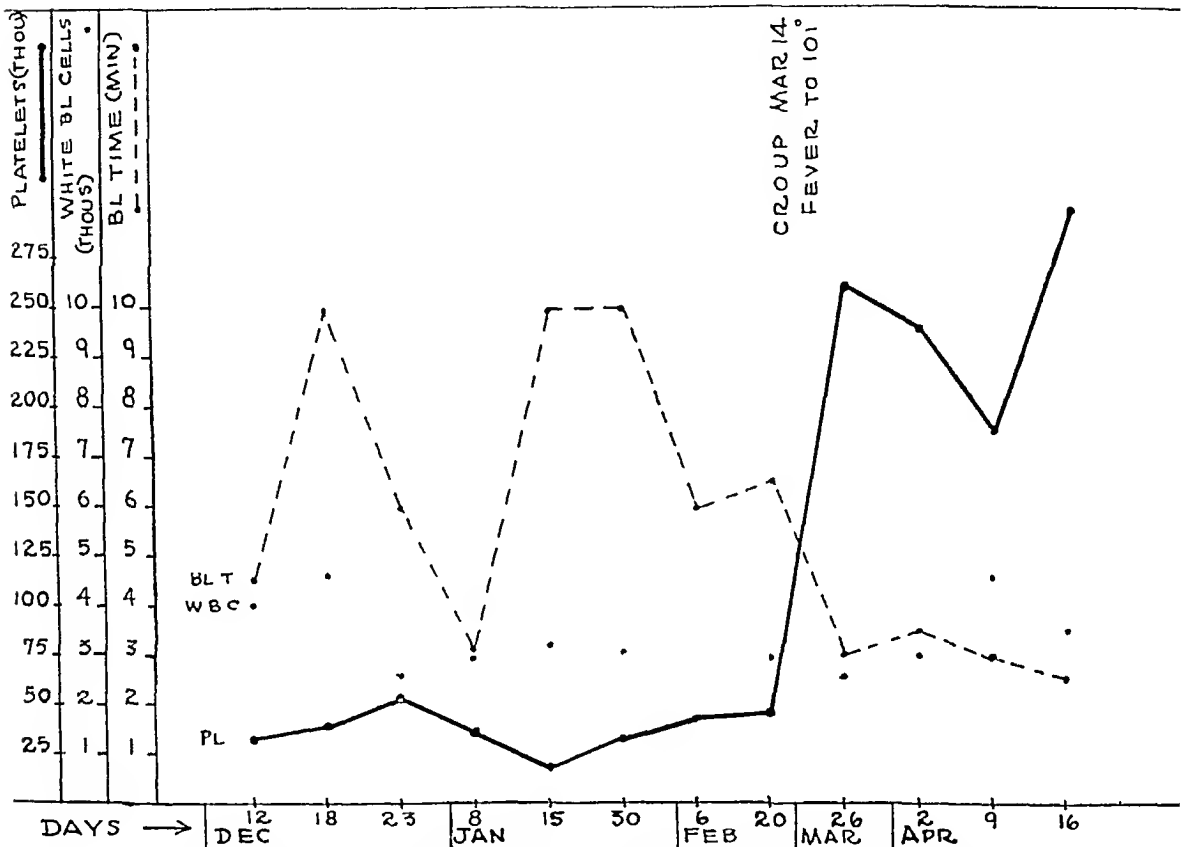


FIG 4 J G (cont'd) Platelets continued at low level until March 14, at which time the child developed croup with temperature rise for a period of 10 days. During this time a platelet rise occurred, which has continued to the present time. The hemorrhagic phenomena also have disappeared.

likely that the so-called roentgen-ray splenectomy is not possible with the doses used in clinical medicine.

DOSAGE

Hippe and Kochmann,⁶ who employed a dose of from 100 R to 180 R, felt that one should not waste time with other forms of treatment in severe thrombopenic bleeding, but should irradiate the spleen at once. They report a marked increase in blood platelets and a cessation of the hemorrhagic phenomena, and quote Nonta who gave 10 doses of 500 R to a five year old girl with this disease with resultant increase in platelets and cessation of the hemorrhage. Thormann⁹ reports the control of hemorrhage in three patients, by means of a dose of 500 R. Costa Storico, using 100 R to 150 R for two to four doses, reports on the cessation of the hemorrhagic phe-

nomena in two patients Mettler⁷ recommends a dosage of 200 R to 300 R daily until 1,200 R to 3,300 R are given in six to 15 days One of his patients had a recurrence of the hemorrhagic phenomena and a reduction of platelets, and a second roentgen-ray series was given with similar good results We note, however, that the patient took the drug Sedoimid each time

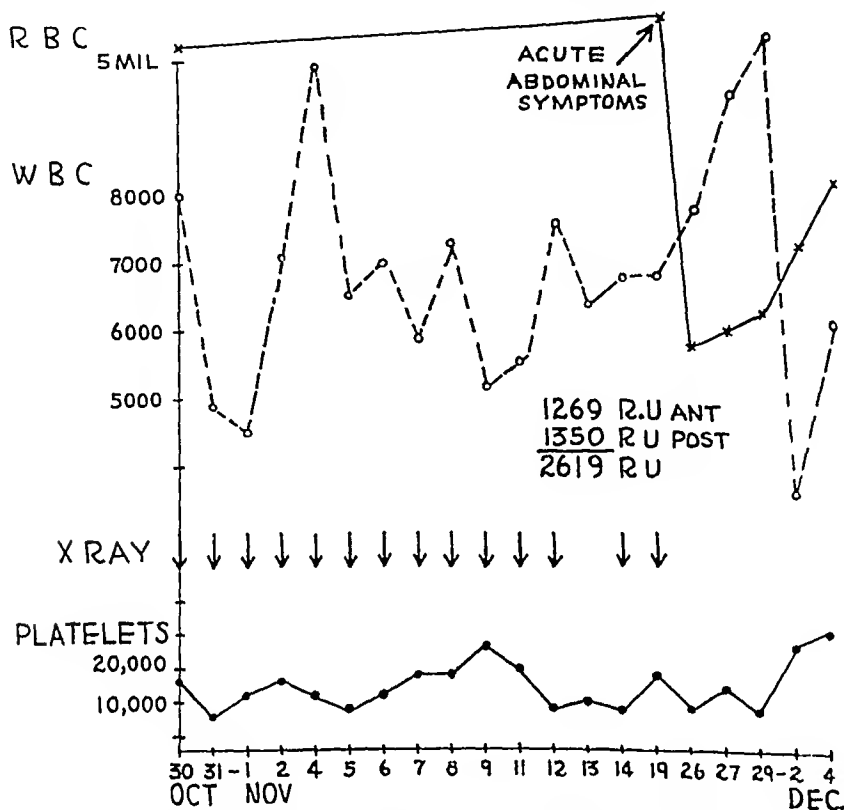


FIG 5 R S Chronic purpura Roentgen-ray to spleen ineffective Acute abdominal pain, marked fall in red cells, and probable intra-abdominal hemorrhage occurred during the treatment A short time later splenectomy was successfully performed Additional treatments to spleen not included in chart bring total to 3591 Rn

before the hemorrhagic phenomena appeared Pancoast, Pendergrass, and Fitz-Hugh⁸ used a dose of approximately 160 R without convincing results

In our series of 11 patients the dose varied from 54 R to 500 R without the favorable results reported by other observers

EVALUATION OF THERAPEUTIC MEASURES

Amatus Lusitanus¹⁵ described the first case of this disease in 1556, and Willan¹⁶ gave it the name of purpura hemorrhagica in 1801 Many therapeutic measures—purging, bleeding, tincture of iron chloride, injections of whole blood, injections of serum, and others, have been enthusiastically recommended In the last few years Peck¹⁷ has used snake venom successfully in this disease, but in our hands it has not been efficacious Anti-

venin has been recommended by Taylor,¹⁸ but we, as well as others, have found it of no value Congo red intravenously, viosterol by mouth, liver extract by mouth and intramuscularly all have their advocates, but in our experience they have not been helpful¹⁹ With regard to liver extract, we

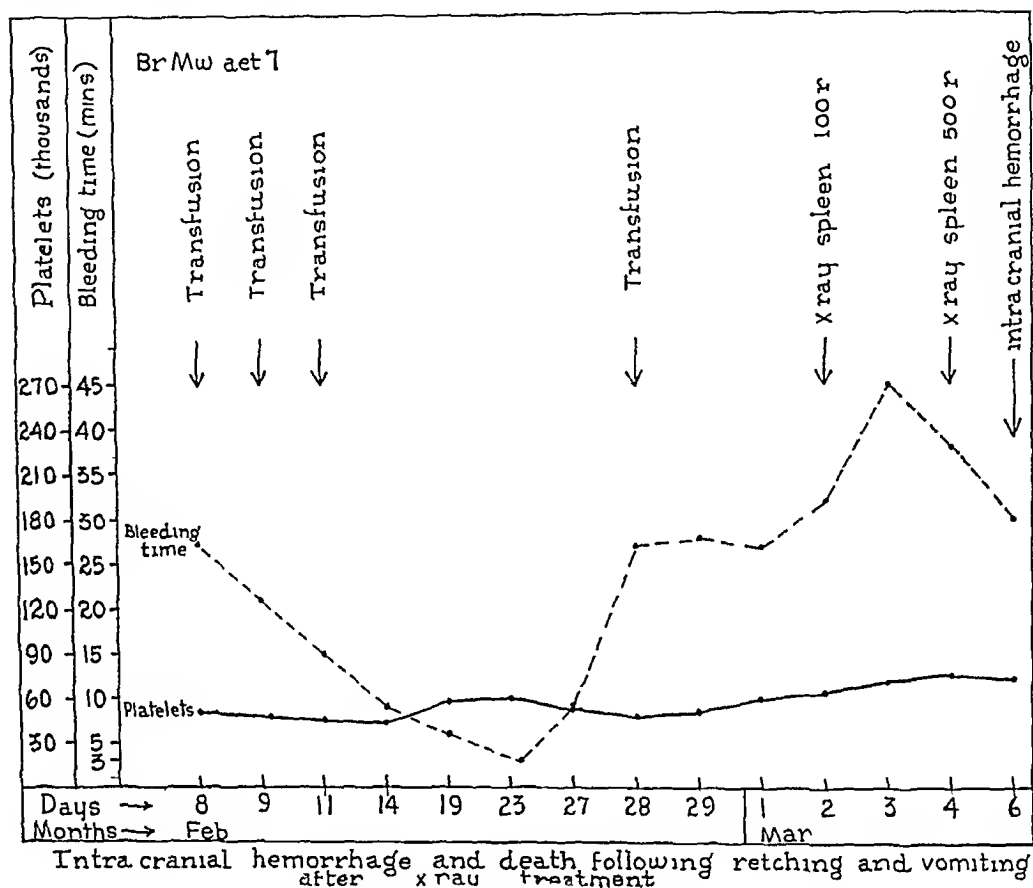


FIG 6 Br M W Acute purpura treated by transfusion with temporary improvement March 2, with bleeding time at 32 minutes, roentgen-ray treatment was administered March 4 a massive dose of roentgen-ray was given, following which retching and vomiting occurred The patient's face became suffused with petechiae at each spasm, intracranial hemorrhage resulted, followed by death

have used it in many patients and have failed to get the results reported by others until recently, when one of our patients developed a satisfactory platelet rise after it had been administered for several days Did the liver extract influence the platelet rise, or was it coincidental? Students of this disease are well aware of the large number of spontaneous cures In our group, 15 patients are included under this heading We have knowledge of two patients, one in extremis, who had a sudden cessation of hemorrhagic phenomena and platelet rise after being anointed, and a second who had a similar experience after a visit from a hex doctor Patients who develop hemorrhagic phenomena and a platelet drop as a result of drug sensitivity frequently have a dramatic increase in platelets after the drug is withdrawn

(Sedormid) As has been pointed out emphatically by Dr J H Pratt,²⁰ whose experience in this disease is very extensive, one must evaluate all forms of treatment in this disease, with particular consideration of the chance of the coincidental spontaneous cure

CASE REPORTS

In this presentation we report on nine patients who we believe received adequate roentgen-ray therapy and three who received the treatment, but not in sufficient amount to be conclusive. In none of these were we able to obtain favorable results comparable to those reported by other observers

DOSAGE

Our erythema dose is considered to be 800 R measured in air. The equipment delivers approximately 54 R per minute measured in air, using a filter of $\frac{1}{2}$ mm of copper, 2 mm of aluminum. Usually the anterior splenic area is rayed one day and the posterior the next. The following is a brief report of the various patients studied with the result as far as the blood findings are concerned. None of the patients studied had a cessation of hemorrhagic phenomena after roentgen-ray therapy

CASE REPORTS

Case 1 C S, male, aged 3

Chief Complaint Spontaneous hematomas, bleeding from nose and ears, petechiae, and ecchymosis

Family History Negative

Past History Symptoms present since one year of age, otherwise negative except for frequent "colds" and middle ear disease

Present Illness One month before admission to the hospital, in 1935, acute hemorrhagic symptoms developed

Physical Examination Spleen and liver not enlarged. General systemic examination negative except for conditions mentioned

Blood Studies

Date	Hgb	R B C	W B C	Platelets	B T (mins)
4/22/35	94	4 90	8 7	22,000 (Cap)	9
	Venous clotting time — 4 mins				
	Roentgen-ray to the spleen anteriorly 153 R				
4/23/35	90	4 80	5 6	26,000	11
	Roentgen-ray to the spleen posteriorly 153 R				
4/24/35	92	4 80	4 8	18,000	10+
	Roentgen-ray to the spleen anteriorly 200 R				
4/25/35	82	4 76	5 8	10,000	9+
	Roentgen-ray to the spleen posteriorly 200 R				
4/26/35	84	4 51	4 2	12,000	10+
4/27/35	Hemorrhagic phenomena more marked, transfusions and other forms of treatment instituted, roentgen-ray discontinued				
8/1/35	88	4 39	8 0	24,000	10+

Diagnosis Chronic purpura hemorrhagica with acute exacerbation. Not benefited by roentgen-ray therapy

Case 2 E E, male, aged 12

Chief Complaint Epistaxis, petechiae, and ecchymosis for three years

Family History Negative

Past History Negative

Admitted October 30, 1935

Physical Examination Petechiae and ecchymosis on face, arms and legs Liver and spleen not palpable

Date	Hgb	R B C	W B C	Platelets	B T (mins)
10/29/35	86	5 56	5 2	40,000	4
10/30/35	Roentgen-ray to the spleen anteriorly 108 R				
	After roentgen-ray to the spleen				
			5 3	20,000	2½
10/31/35	Before roentgen-ray to the spleen				
	95	5 24	5 7	16,000	1½
	Roentgen-ray to the spleen posteriorly 108 R				
	After roentgen-ray to the spleen				
			4 8	18,000	2½
11/1/35	Before roentgen-ray to the spleen				
	103	5 51	3 2	12,000	7
	Roentgen-ray to the spleen anteriorly 180 R				
11/2/35	Before roentgen-ray to the spleen				
	98	5 69	5 3	18,000	3½
	Roentgen ray to the spleen anteriorly 108 R				
	Roentgen-ray to the spleen posteriorly 108 R				
11/5/35	Roentgen-ray to the spleen anteriorly 108 R				
	Roentgen-ray to the spleen posteriorly 108 R				
11/6/35	Roentgen-ray to the spleen anteriorly 108 R				
	Roentgen-ray to the spleen posteriorly 108 R				
11/9/35	Before roentgen-ray to the spleen				
	105	6 03	3 5	20,000	2½
	Roentgen-ray to the spleen posteriorly 108 R				
	After roentgen-ray to the spleen				
			6 1	14,000	2
11/13/35	Roentgen-ray to the spleen anteriorly 108 R				
11/14/35	Before roentgen-ray to the spleen				
	100	5 73	5 9	20,000	4
	Roentgen-ray to the spleen posteriorly 108 R				
	After roentgen ray to the spleen				
			4 8	6,000	1½
11/16/37	98	6 005	4 2	26,000	2
	Roentgen-ray to the spleen anteriorly 108 R				
11/19/35	102	5 41	4 4	10,000	5½
	Roentgen-ray to the spleen posteriorly 108 R				
11/21/35	104	5 62	3 8	38,000	6
	Roentgen-ray to the spleen anteriorly 108 R				
	Roentgen-ray to the spleen posteriorly 108 R				
11/23/35			4 3	8,000	10
	Roentgen-ray to the spleen anteriorly 108 R				
	Roentgen-ray to the spleen posteriorly 108 R				
11/26/35			4 2	18,000	7
	Roentgen-ray to the spleen anteriorly 108 R				
	Roentgen-ray to the spleen posteriorly 108 R				
12/3/35			4 0	24,000	2½
	Roentgen-ray to the spleen anteriorly 108 R				
	Roentgen-ray to the spleen posteriorly 108 R				
	After roentgen-ray to the spleen				
			6 4	38,000	4
12/5/35	89	4 91	5 6	16,000	6
12/19/35	96	5 37	6 3	24,000	3
5/25/36	96	5 002	2 8	18,000	12

Diagnosis Chronic purpura hemorrhagica Roentgen-ray treatment ineffective

Case 3 J M, male, aged 10

Chief Complaint Bruising, nose bleed

Family History Negative

Past History Measles, easy bruising in 1932 Patient states that he had nose bleed at the change of seasons The hemorrhage was so severe at times that he became unconscious He states that he does not bruise unless he injures himself

Admitted May 18, 1937

Blood Studies

Date	Hgb	R B C	W B C	Platelets	BT (mins)
5/18/37	79	4 45	8 7	34,000 (Cap) 58,000 (Ven)	10+
	Venous clotting time—5				
5/19/37	82	5 13	8 1	34,000 (Cap)	10+
	Roentgen-ray to the spleen anteriorly 200 R				
5/20/37	Roentgen-ray to the spleen posteriorly 200 R				
5/21/37	95	5 21	8 8	40,000 (Cap) 42,000 (Ven)	6½
	Roentgen-ray to the spleen anteriorly 250 R				
5/22/37	104	5 13	6 1	50,000 (Cap)	3½
5/24/37	81	4 50	4 9	8,000 (Cap) 14,000 (Ven)	10+
	Roentgen-ray to the spleen anteriorly 250 R				
5/25/37	83	4 07	4 8	12,000 (Cap) 14,000 (Ven)	10+
	Roentgen-ray to the spleen posteriorly 300 R				
5/26/37	88	4 44	5 0	16,000 (Cap) 22,000 (Ven)	10+
5/29/37	87	4 74	4 0	20,000 (Cap) 20,000 (Ven)	2½
8/9/37	85	4 80	8 6	21,000 (Cap) 24,000 (Ven)	10+

Diagnosis Chronic purpura hemorrhagica with acute exacerbation Roentgen-ray treatment ineffective for control of hemorrhagic phenomena and increase in platelets

Case 4 J C, male, aged 14

Chief Complaint Bleeding from nose, petechiae, and ecchymosis (general)

Family History Negative

Past History Chicken pox and measles In 1928 patient was hospitalized because of repeated nose bleed The nose bleed, petechiae and ecchymoses continued at various intervals until 1936, when patient was admitted to another hospital, at which time the blood loss from the nose was unusually severe following a cold There was some bleeding from the gums at this time

Present Illness On admission, February 15, 1937, the patient had been bleeding from the nose for some days There was marked ecchymosis of the arms and legs and bleeding from the gums The spleen was palpable, the liver not felt

Blood Studies See chart

Date	Hgb	R B C	W B C	Platelets	B T (mins)
2/15/37	71	3 45	9 9	10,000	12
	Roentgen-ray to the spleen anteriorly 102 R				
2/16/37				Roentgen-ray to the spleen posteriorly 102 R	
2/17/37	46	2 40	7 0	16,000	3
2/18/37				Roentgen-ray to the spleen anteriorly 153 R	
	43	2 63	3 6	26,000	6
2/19/37				Roentgen-ray to the spleen anteriorly 102 R	
	37	2 18	5 8	16,000	5
2/20/37				Roentgen-ray to the spleen posteriorly 153 R	
	38	2 27	5 4	26,000	4½
2/23/37				Roentgen-ray to the spleen posteriorly 153 R	
	52	2 87	9 5	8,000	15
2/25/37				Roentgen-ray to the spleen anteriorly 153 R	
	53	2 81	7 8	16,000	8
2/26/37				Roentgen-ray to the spleen posteriorly 153 R	
2/27/37	46	2 49	7 2	18,000	4½
3/1/37	40	2 84	6 2	12,000 (Cap)	½
				46,000 (Ven)	
3/4/37	45	2 68	5 8	20,000 (Cap)	9
				61,000 (Ven)	
3/20/37				Roentgen-ray to the spleen anteriorly 208 R	
	64	3 17	4 0	6,000 (Cap)	
				21,000 (Ven)	10+
3/23/37				Roentgen-ray to the spleen posteriorly 262 R	
	70	3 72	4 1	22,000 (Cap)	
				26,000 (Ven)	
3/24/37	Splenectomy				

Diagnosis Chronic purpura hemorrhagica with acute exacerbation Roentgen-ray treatment ineffective

Case 5 R C, male, aged 7

Chief Complaint Weakness, bleeding from gums, ecchymoses, and petechiae

Family History Negative

Past History Measles, pertussis, pneumonia, frequent attacks of tonsillitis
Tonsillectomy two years previously, no excessive bleeding

Present Illness Admitted June 1, 1926 Patient, bleeding extensively from gums, fell in the street and was brought to the hospital

Physical Examination Gums oozing, legs and thighs covered with ecchymoses and petechiae Spleen is palpable, liver not felt

July 16, after treatment with transfusions, roentgen-ray therapy was administered in a dose of approximately 540 R Unfortunately no platelet counts are available on this day The last platelet count recorded was on June 23, at which time the platelets were 88,000 On June 21 the hemoglobin was 88 per cent red blood cells 4,700,000, white blood cells 6,400, platelets 334,000

The patient was improving continually at the time of roentgen-ray Hemorrhagic phenomena had disappeared and the platelets were increasing In our opinion there was no indication for roentgen-ray therapy, nor was there indication for splenectomy, which was performed on the 28th of July The patient died November 23, 1926, during a re-admission to the hospital, when a diagnosis of osteomyelitis and broncho-pneumonia was made

Case 6 J D, male, aged 53

Chief Complaint Epistaxis

Family History Negative

Past History Smallpox at 5, bruised easily for the past 8 or 9 years

Present Illness November 1933 spontaneous nose bleed Admitted to the hospital January 27, 1934 A cold in the head brought on a severe hemorrhage January 26 On admission purpuric spots were present in the mouth and the extremities and there was bleeding from both nasal passages Various forms of treatment were used—transfusion, liver extract, snake venom, and others

Blood Studies

Date	Hgb	R B C	W B C	Platelets	B T (mins)
3/19/34	80	4 20	8 6	16,000	10+
3/20/34	Roentgen-ray to the spleen anteriorly 108 R				
3/21/34	80	4 20	7 2	16,000	10+
3/22/34	Roentgen-ray to the spleen anteriorly 162 R				
3/23/34	84	4 42	8 2	20,000	10+
3/26/34	Roentgen-ray to the spleen anteriorly 162 R				
3/27/34	Roentgen-ray to the spleen anteriorly 162 R				
	85	4 60	5 6	18,000	10+
3/28/34	Roentgen-ray to the spleen posteriorly 108 R				
3/29/34	80	4 16	4 8	10,000	10+
3/30/34	Roentgen-ray to the spleen posteriorly 162 R				
3/31/34	Roentgen-ray to the spleen posteriorly 162 R				
	80	4 30	4 0	16,000	10+
4/2/34	82	4 70	4 8	15,000	10+

Diagnosis Chronic purpura hemorrhagica with acute exacerbation Roentgen-ray treatment ineffective

Case 7 P S, female, aged 45

Admitted March 1921, in extremis, bleeding from mucous membranes, nose, mouth, vagina Ecchymoses and petechiae were present

Her hemoglobin was 30 per cent, red blood cells 2,000,000, white blood cells 8,600, platelets 16,000 Roentgen-ray was administered over the spleen in a dose of 500 R, but she died in 48 hours, although transfusions were used

Case 8 R S, female, aged 23

Chief Complaint Bleeding from nose and gums since age 6, excessive menstruation since age 14, tendency to bruise easily since age 6, long bleeding from cuts since age 6, weakness, dyspnea and palpitation, and swelling of ankles for three years

Family History Negative

Past History Measles, pertussis, frequent headaches, tendency to head colds Tonsils treated by electro-coagulation six years ago

Present Illness Admitted Oct 1935 Frequent spontaneous nose bleed since age of 6, occurring daily until onset of menses, then about one every two weeks, lasting one to two hours At age of 20 the nose bleed occurred once a month Spontaneous bleeding from the gums since age 21 Fourteen teeth have been extracted in the last two years, bled two to four days after each extraction

Physical Examination Spleen slightly enlarged, liver not palpable Petechiae and ecchymoses present on lower extremities Some tenderness in right lower quadrant

Roentgen-ray treatments daily from October 30 to November 12, except Sundays Seven anterior spleen 216 R, one 162 R, one 108 R, one 135 R Seven posterior spleen, five at 216 R, one at 162 R, one at 108 R One lateral spleen at 108 R, one left and right lateral chest 108 R each

Blood Studies See chart

Date	Hgb	R B C	W B C	Platelets	B T (mins)
10/14/35		5 09		16,000	3½
10/30/35	Before roentgen-ray to the spleen				
	76	5 12	7 5	16,000	7½
	After roentgen-ray to the spleen			18,000	10+
10/31/35	Before roentgen-ray to the spleen				
	76	5 03	4 9	6,000	10+
	After roentgen-ray to the spleen			14,000	9½
11/1/35	Before roentgen-ray to the spleen				
	70	4 71	4 5	12,000	5
	After roentgen-ray to the spleen			10,000	9½
11/2/35	Before roentgen-ray to the spleen				
	80	5 30	7 1	16,000	1½
	After roentgen-ray to the spleen			18,000	15+
11/4/35	Before roentgen-ray to the spleen				
		5 10	9 9	12,000	10+
	After roentgen-ray to the spleen			18,000	4
11/5/35	Before roentgen-ray to the spleen				
			6 5	8,000	3½
11/6/35	Before roentgen-ray to the spleen				
		5 35	7 1	12,000	10+
	After roentgen-ray to the spleen			24,000	8½
11/7/35	Before roentgen-ray to the spleen				
	81	5 44	5 8	18,000	8
	After roentgen-ray to the spleen			12,000	6½
11/8/35	Before roentgen-ray to the spleen				
		5 45	7 3	18,000	8½
11/9/35	After roentgen-ray to the spleen				
		4 71	5 2	26,000	4½
11/11/35	Before roentgen-ray to the spleen				
			5 6	20,000	2
	After roentgen-ray to the spleen			12,000	6
11/12/35	Before roentgen-ray to the spleen				
			7 6	8,000	10+
11/13/35	Before roentgen-ray to the spleen				
		5 21	6 4	10,000	5½
11/14/35	Before roentgen-ray to the spleen				
		5 07	6 8	8,000	7½
	After roentgen-ray to the spleen				
			6 6	16,000	10+
11/19/35		5 28	6 8	18,000	7½
11/26/35	47	2 97	7 8	8,000	9½
11/30/35	53	3 01	6 8		
12/4/35	64	4 13	6 1		
12/9/35	60	3 49	4 9	6,000	10+
12/20/35	Before roentgen-ray to the spleen				
	70	4 79	6 1	16,000	10+
	After roentgen-ray to the spleen			22,000	
12/21/35	Before roentgen-ray to the spleen				
		4 70	5 5	16,000	
	After roentgen-ray to the spleen			16,000	7½
12/23/35	Before roentgen-ray to the spleen				
		3 79	4 1	16,000	4½

Date	Hgb	R B C	W B C	Platelets	B T (mins)
	After roentgen-ray to the spleen				
				10,000	
1/2/36		5 01	6 3	24,000	6½
2/4/36		4 45		14,000	10+
2/10/36	52	4 09	5 6	25,000	9
2/11/36	52	4 09	3 9	10,000	20
	Splenectomy 3 30 p m				
	After splenectomy—5 00 p m				
	62	4 54	19 9	68,000	15
2/12/36	52	3 61	44 0	378,000	1
2/13/36	46	3 18	24 0	722,000	15
2/14/36	48	3 43	12 7	886,000	2½
2/15/36	52	3 69	12 1	1,320,000	3½
2/17/36	53	4 02		2,366,000	1½
2/21/36	50	3 18	7 6	2,120,000	3
2/26/36		3 50		1,620,000	15
3/3/36	55	3 75		464,000	3½
3/9/36	51	3 54	6 0	292,000	1
3/13/36		4 00		222,000	1
3/26/36	51	3 53	8 0	366,000	½
4/8/36	68	4 76	6 4	251,000	1½

Diagnosis Chronic purpura hemorrhagica Roentgen-ray treatment ineffective

Comment On October 19, following roentgen-ray to the spleen, the patient developed acute abdominal pain associated with marked fall in red cells of more than 2,000,000 per cubic mm. There was distinct abdominal tenderness, rise in temperature, and an increase in the white cell count above her usual level. The differential count showed a decided shift to the left. We felt that she may have had an intra-abdominal hemorrhage as there was evidence of free fluid in the abdominal cavity. The roentgen-ray treatments were discontinued.

Case 9 J. G., female, aged four

Chief Complaint Easy bruising, nose bleed

Family History Negative

Past History Always healthy until present illness

Present Illness Admitted October 1935. At two years of age child had severe infection involving nose, throat, and sinuses. This condition was present for four or five weeks. Since then she has bruised easily, has had many head colds with frequent nose bleed and one profuse hemorrhage from bowel.

Physical Examination Bruises and petechiae present on the arms, lower extremities and the body. Spleen and liver are both palpable, although not materially enlarged.

Blood Studies See charts 3 and 4

Date	Hgb	R B C	W B C	Platelets	B T (mins)
10/9/35	73	4 63	6 5	30,000	4
10/10/35	Before roentgen-ray to the spleen				
	79		7 0	24,000	3½
10/11/35	Roentgen-ray to the spleen anteriorly and posteriorly				
	108 R				
	After roentgen-ray to the spleen				
	73	4 12	7 8	32,000	3½
10/12/36	Roentgen-ray to the spleen anteriorly and posteriorly				
	108 R				
	Before roentgen-ray to the spleen				
	75	4 41	9 3	20,000	5
	After roentgen-ray to the spleen				
				60,000	3½
10/14/35	Before roentgen-ray to the spleen				
	80	4 65	4 6	54,000	4
	After roentgen-ray to the spleen				
			5 9	86,000	10+

Date	Hgb	R B C	W B C	Platelets	B T (mins)
10/15/35	Before roentgen-ray to the spleen				
	97	4 52	5 6	78,000	3
	After roentgen-ray to the spleen			54,000	12+
10/16/35	Before roentgen-ray to the spleen				
		5 08	3 8	70,000	2
	After roentgen-ray to the spleen			64,000	10+
10/17/35	Before roentgen-ray to the spleen				
	84	4 93	16 7	152,000	3
	After roentgen-ray to the spleen			206,000	
10/18/35	Before roentgen-ray to the spleen				
	86	4 70	9 4	168,000	2½
	After roentgen-ray to the spleen			126,000	2
10/19/35	Before roentgen-ray to the spleen				
		4 96	6 8	86,000	7½
	After roentgen-ray to the spleen			144,000	5½
10/21/35	Before roentgen-ray to the spleen				
		4 17	8 2	120,000	4
	After roentgen ray to the spleen			94,000	10+
10/22/35	Before roentgen-ray to the spleen				
	81	4 81	8 9	94,000	3
	After roentgen-ray to the spleen			76,000	10
10/23/35	Before roentgen-ray to the spleen				
	82	5 19	8 4	88,000	6
	After roentgen-ray to the spleen			134,000	3½
10/24/35	Before roentgen-ray to the spleen				
	80	5 53	8 3	116,000	5
	After roentgen-ray to the spleen			160,000	3
10/25/35	Before roentgen-ray to the spleen				
		5 60	9 1	168,000	3
	After roentgen-ray to the spleen			172,000	5½
10/26/35	Before roentgen-ray to the spleen				
	80	4 53	7 2	144,000	5½
	After roentgen-ray to the spleen			200,000	1
10/28/37	Before roentgen-ray to the spleen				
	75	4 77	9 4	218,000	2
	After roentgen-ray to the spleen			176,000	2½
10/29/35	Before roentgen-ray to the spleen			144,000	5
10/30/35	Roentgen-ray anteriorly and posteriorly 108 R				
	Before roentgen-ray to the spleen				
		4 13	6 1	140,000	5½
11/9/35	After roentgen-ray to the spleen			142,000	½
	Roentgen-ray anteriorly and posteriorly 108 R				
	Before roentgen-ray to the spleen				
11/13/35				74,000	6
	Roentgen-ray anteriorly and posteriorly 108 R				
	Before roentgen-ray to the spleen				
				74,000	5½
	After roentgen-ray to the spleen			13,000	5
11/16/35	Roentgen-ray anteriorly and posteriorly 108 R				
	Before roentgen-ray to the spleen				
		4 52	3 7	60,000	3½
	After roentgen-ray to the spleen			60,000	3½

Date	Hgb	R B C	W B C	Platelets	B T (mins)
11/20/35	Roentgen-ray anteriorly and posteriorly 108 R				
	Before roentgen-ray to the spleen				
		4 11	4 7	94,000	5
	After roentgen-ray to the spleen				
			3 5	84,000	2
11/27/35	Roentgen-ray anteriorly and posteriorly 108 R				
	Before roentgen-ray to the spleen				
		4 31	4 0	6,000	7
	After roentgen-ray to the spleen				
			3 4	6,000	4
12/12/35	75	3 72	2 7	32,000	4½
12/18/35		3 66	4 6	38,000	10
12/23/35		4 24	2 6	54,000	6
1/15/36		4 52	3 3	18,000	10
2/20/36		4 74	2 9	46,000	6½
Croup March 14, 1936 Fever to 101° Sick 10 days					
3/26/36		4 27	2 6	260,000	3
4/2/36	83	4 44	3 0	238,000	3½
4/9/36		5 11	4 6	188,000	3
4/16/36	80	3 91	3 5	292,000	2½
4/30/36				206,000	
5/8/36	77	3 86	2 9	188,000	3
5/12/36	76	4 22	3 3	174,000	
3 injections of liver extract					
5/26/36		5 14	4 0	252,000	2½

Thirty roentgen-ray treatments to the spleen anteriorly and posteriorly, total 1,620 R

The rise in blood platelets which occurred from October 14 to October 17 was followed by a drop from that date until October 23, at which time they rose to a high point of 218,000 on the 28th of October. From this time on, in spite of roentgen-ray treatment, the platelets fell to a low level of 6,000 on November 27. The white blood cells also dropped to a level of 2,700, and it was decided to discontinue roentgen-ray therapy. It seemed at that time that the roentgen-ray was bringing about a rise in blood platelets and the roentgen-ray treatment was discontinued from the 30th of October until November 9. From that time on there was no favorable effect from the use of roentgen-ray.

It would seem to us that this patient should be included along with the others as roentgen-ray treatment ineffective. Possibly a more optimistic observer might include this one patient under the heading of "questionable roentgen-ray effect."

Case 10 E S, male, aged 7

Chief Complaint Recurrent nose bleed for five months

Family History Negative

Past History Pertussis, mumps, varicella, pneumonia

Present Illness Admitted March 1936. Began to bruise easily at 5 years of age. The summer of 1935 he was in another hospital and was transfused repeatedly. Since September 1935 has had slight attacks of nose bleed, but in the last two weeks he had 6 severe attacks, one on the morning of admission.

Physical Examination There is bleeding from the left nasal passage anteriorly and posteriorly. Tonsils are large and seem to be infected. Spleen and liver are not felt. Petechiae and ecchymosis are present.

Blood Studies

Date	Hgb	R B C	W B C	Platelets	B T (mins)
3/30/36	32	2 59	16 0	10,000	15+
	Venous clotting time normal				
	Transfusion 120 c c				
3/31/36	38	2 45	9 6	28,000	15+
4/1/36	39	2 27	9 2	22,000	
	Transfusion 120 c c				
	After transfusion				
	44	2 84	12 3	22,000	15+
4/2/36	42	2 92	8 5	32,000	15+
4/4/36	45	3 07	10 2	32,000	
4/6/36		2 26	8 7	14,000	
	Occasional giant platelet seen				
4/7/36	51	3 10	10 3	6,000	12+
	Transfusion 120 c c				
	After transfusion				
	54	3 14		18,000	15+
4/9/36	54	3 44	6 7	10,000	
	Transfusion 120 c c				
	After transfusion				
	60	3 72	8 2	26,000	10+
4/11/36		Transfusion 120 c c			
	After transfusion				
	60	4 02	7 7	4,000	15+
4/14/36	58	3 91	11 0	28,000	15+
4/15/36		Transfusion 120 c c			
	After transfusion				
	70	4 00	12 6	10,000	15+
4/17/36	63	4 03	8 3	8,000	Long
	Roentgen-ray anterior spleen 108 R				
	Roentgen-ray posterior spleen 108 R				
4/18/36	Transfusion 120 c c , different donor				
	After transfusion				
	71	4 23	9 2	20,000	
4/20/36	69	4 78	7 2	8,000	15+
	Roentgen-ray anterior spleen 108 R				
	Roentgen-ray posterior spleen 108 R				
4/21/36	Transfusion 120 c c				
	After transfusion				
	77	4 81	6 3	14,000	6½
	Roentgen-ray anterior spleen 108 R				
	Roentgen-ray posterior spleen 108 R				
4/22/36	72	4 37	6 2	8,000	15+
4/23/36	76	5 19	7 0	8,000	15+
4/24/36	72	4 24	5 6	26,000	8¾
	Roentgen-ray anterior spleen 108 R				
4/27/36	72	4 65	5 4	10,000	15+
4/29/36	60	3 40	5 4	8,000	Prolonged
	Roentgen-ray anterior spleen 135 R				
	Roentgen-ray posterior spleen 135 R				
5/1/36	53	3 07	3 5	8,000	15+
5/2/36	60	3 34	6 8	8,000	10+
	Transfusion				
5/4/36	62	3 54	7 1	6,000	15+
	Transfusion				
5/6/36	65	3 56	6 9	22,000	
5/9/36		Transfusion			
	After transfusion				
	70	3 60	4 7	16,000	10+

Date	Hgb	R B C	W B C	Platelets	B T (mins)
5/11/36	70	4 24	5 1	26,000	Prolonged
	Snake venom				
5/12/36	72	4 00	3 1	2,000	10
	Transfusion				
5/13/36	73	3 93	3 7	8,000	7
	Snake venom				
5/15/36	Transfusion				
	After transfusion				
	73	4 78	4 8	10,000	15+
5/18/36	67	3 74	5 6	18,000	15+
	Snake venom				
5/19/36		3 32	5 5	12,000	9
5/22/36	Transfusion				
	After transfusion				
	70	3 90	5 3	10,000	15+
6/1/36	71	4 26	6 1	48,000	10+
6/3/36	66	3 38	5 8	12,000	15+
6/5/36	62	3 33	3 9	36,000	15+
6/6/36	61	3 34	4 1	18,000	15+
	Transfusion				
	Snake venom				
6/8/36	63	3 97	8 1	6,000	10½
	Transfusion				
6/11/36	73	3 82	4 2	24,000	15+

Roentgen-ray treatment ineffective with regard to control of hemorrhagic phenomena and platelet increase

Diagnosis Chronic purpura hemorrhagica with acute exacerbation

Case 11 J P, female, aged 12

Chief Complaint Easy bruising, nose bleed

Family History Negative

Past History German measles, mumps, tonsils and adenoids removed at age 7, no excessive bleeding Patient admitted September 1935 The first evidence of this disease occurred June 1935, petechiae were present on both ankles Easy bruising had been present two or three weeks previous Patient treated in another hospital by transfusions, injections of whole blood, and intramuscular injection of pentnucleotide

Physical Examination This examination revealed the presence of petechiae, ecchymoses, spleen and liver not enlarged

Blood Studies See chart

Date	Hgb	R B C	W B C	Platelets	B T (mins)
7/30/35	80	4 84	13 0	8,000	20
8/6/35	77	4 35	10 0	24,000	10
9/3/35	84	4 38	10 9	12,000	8
9/23/35	80	4 25	7 1	14,000	10
9/25/35	85	4 19	12 9	None seen	11½
	Beginning of roentgen-ray treatments to spleen				
	After			34,000	5
9/26/35	Before roentgen-ray treatment to the spleen				
	78	4 45	5 7	8,000	6½
	After roentgen-ray treatment to the spleen				
		4 10		12,000	10
9/27/35	Before roentgen-ray treatment to the spleen				
	80	4 09	7 0	8,000	10
9/28/35	Before roentgen ray treatment to the spleen				
		4 15	6 0	6,000	4
	After roentgen-ray treatment to the spleen				
				12,000	6
10/2/35	Before roentgen-ray treatment to the spleen				
	85	4 42	5 0	52,000	10
	After roentgen-ray treatment to the spleen				
				12,000	5

Date	Hgb	R B C	W B C	Platelets	B T (mins)
10/5/35	Before roentgen-ray treatment to the spleen				
	75	4 53	4 2	48,000	9
	After roentgen-ray treatment to the spleen				
				40,000	8 $\frac{1}{2}$
10/7/35	Before roentgen-ray treatment to the spleen				
	76	4 54	5 1	22,000	4 $\frac{1}{2}$
	After roentgen-ray treatment to the spleen				
				28,000	10+
10/15/35	Before roentgen-ray treatment to the spleen				
	78	4 20	5 5	10,000	5
	After roentgen-ray treatment to the spleen				
				14,000	7
10/26/35	75	4 53	3 5	20,000	10
11/2/35		3 28	4 0	12,000	4 $\frac{1}{2}$
11/9/35		4 99	4 5	28,000	4 $\frac{1}{2}$
11/23/35		4 71	3 2	12,000	4 $\frac{1}{2}$
12/6/35	88	4 81	4 4	36,000	7
12/21/35		4 50	4 0	28,000	
1/4/36		4 41	4 3	20,000	2
1/11/36		4 25	4 7	52,000	2
1/18/36		4 68	5 6	22,000	10

Roentgen-ray treatments given daily from September 25, 1935, to October 15, 1935 (except September 29, October 6, 8, and 13) on spleen, alternating every other day from anterior to posterior Seventeen treatments given Total of 1,431 R units on anterior and 1,188 R units on posterior

Diagnosis Subacute purpura hemorrhagica Roentgen-ray ineffective

DISCUSSION

It is evident from this study that the response to roentgen-ray in the patients which we present has been ineffective One might stretch a point and give credit to the roentgen-ray for an increase in platelets in one patient (J G), but this platelet increase did not hold and was not continued after further roentgen-ray treatment

Mettier recommends a dosage of from 200 R to 300 R It is true that we have not given this dosage to all of our patients However, other observers have obtained results comparable to those of Mettier with a smaller dose In many of our patients we have administered large doses, that is, 200 R without favorable response It seems fair to conclude that we have given roentgen-ray a suitable trial in the patients who came under our direction The response has been disappointing

Viewing the subject from a broader standpoint, we draw attention to brilliant reports as to cessation of hemorrhagic phenomena and improvement in the platelet numbers by other observers using various forms of treatment, for example, Herron and MacElroy¹⁹ obtained excellent results using auto-lyzed liver extract (Squibb) by mouth In our experience, with one exception, and this result is questionable, we were unable to duplicate their results We do not doubt the results which Mettier and some others have obtained We do, however, disagree with the statement that roentgen-ray to the spleen in suitable dosage is a satisfactory method of controlling hemorrhagic phenomena and of increasing the number of blood platelets We assert that this is an unfortunate statement for it leads the general medical

public to assume that all cases of idiopathic hemorrhagic purpura will be affected favorably if adequate roentgen-ray dosage is administered to the spleen. It seems probable that there are certain patients with this disease who will respond in a manner such as described by Mettier and others, and that there are other patients with the same disease who will fail to respond to adequate roentgen-ray treatment.

When this paper was read before the Section on Medicine of the College of Physicians of Philadelphia, Dr Fitz-Hugh, in the discussion, stated that he felt the only satisfactory treatment for this disease was splenectomy. Such a statement is, in our opinion, just as unjustifiable as that which Mettier makes with regard to the use of roentgen-ray. At present there is no single treatment for this disease that is eminently satisfactory. Students of this condition know that many patients who have been splenectomized have recurrences. Our plan of treatment is as follows:

If the patient is not in a dangerous state from loss of blood, we give him an opportunity to recover without any special form of treatment. If there is a considerable anemia or a progressive anemia, small transfusions are used. These are given every two or three days, or at times more often, or in larger doses. Vitamin C intravenously is given in selected cases. Liver extract intramuscularly and by mouth is also used. We intend to continue the use of snake venom and roentgen-ray in sufficient dose in all patients in whom we think it is safe, and finally, when all other measures fail we resort to splenectomy.

We wish to call attention again to the danger of roentgen-ray therapy, as is suggested by the effect which we noted in two of our patients: one, R S, who had an acute intra-abdominal condition with a sudden drop in red blood cells following roentgen-ray therapy, and second, the patient with a long bleeding time, who developed intracranial hemorrhage and died after roentgen-ray treatment, probably as a result of retching and vomiting (chart 6).

CONCLUSIONS

1 Roentgen-ray treatment to the spleen in adequate dosage is not a satisfactory form of treatment in all patients with this disease.

2 Purpura hemorrhagica is a disease in which spontaneous cure is frequently seen.

3 Many forms of treatment have been set forth as efficacious in this disease, but when tried by others have been found to be useless.

4 Patients receiving roentgen-ray therapy may become nauseated and vomit. This increases intracranial pressure and intracranial hemorrhage may result, especially if the bleeding time is long.

5 It seems probable that the patients with this disease may fall into a variety of groups, depending upon their response to various forms of treatment. One observer may be successful with a certain form of treatment in a few patients and another observer may be unsuccessful because he is not treating that particular variety of purpura hemorrhagica.

6 Roentgen-ray therapy in this disease, in dosage as set forth by Metier, should be used in selected cases, with the knowledge that it may not be efficacious in the particular patient under treatment

7 An estimation of the platelets in venous as well as in cutaneous blood may be of help in explaining some of the discrepancies between bleeding time, hemorrhagic phenomena, and platelet number

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THE EFFECTS OF INSULIN HYPOGLYCEMIA UPON THE DIABETIC HEART IN CHILDREN AND YOUTH *

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INTRODUCTION

THE possibility that harmful effects upon the heart may be produced in diabetic patients by the use of insulin has rested upon the occasional anginal attack after the administration of insulin to cardiac patients. Transitory changes in the electrocardiogram have been noted after the administration of insulin, suggesting some change in the heart muscle. It must be remembered that the injection of insulin into the body in a sufficient quantity to produce hypoglycemia, brings about changes, varying with the individual, the amount of insulin injected, the state of the counter-regulatory system, and undoubtedly other factors. When the blood sugar reaches a sufficiently low level, an increased output of adrenalin occurs, raising the blood pressure, increasing the pulse rate, stimulating the metabolism and tending to counteract the hypoglycemia by the liberation of glucose from the glycogen in the liver. The possibility that these effects may be dangerous in a patient with a heart seriously damaged by coronary disease has been emphasized disproportionately and little attention drawn to the probability of the generally advantageous effect of insulin properly administered. Whether there is any harmful effect upon the healthy heart is an entirely different question.

In this paper are reported the results of a series of electrocardiograms taken in young patients receiving insulin. Attempts were made to obtain electrocardiograms when the blood sugar was high as well as during a period when the blood sugar was low, but before serious symptoms of insulin shock had occurred. In several of the patients mild insulin reactions did occur a few minutes after the electrocardiogram had been taken (usually between 11:30 a.m. and 12 o'clock noon). The object was not to demonstrate effects produced by serious or extensive hypoglycemia with unconsciousness or convulsions but rather to observe changes, if any, occurring during the rapid reduction of the blood sugar by means of injected insulin.

In addition to these observations upon the electrocardiograms of young patients, one patient is reported who was seen in consultation by the writer after she had received by error an overdose of insulin which proved to be fatal. A complete autopsy was made and the results are here summarized.

* Received for publication August 16, 1937

ELECTROCARDIOGRAPHIC DATA

The patients were 13 males and 12 females, varying in age from seven years to 46 years, only two were over 25 years of age. None of these patients gave a history of rheumatic fever or of any infection usually related to heart disease, nor in any of these cases was there clinical evidence of any cardiac lesion. The duration of diabetes in these cases varied from 0.1 year to 14.2 years.

Electrocardiograms were taken with the three conventional leads and a fifth lead from the cardiac apex to the left leg, these are summarized in table 1.

The electrocardiograms were taken usually after breakfast in the morning and again shortly before noon, except in those instances where only a single record is available. Immediately after the electrocardiograms were taken, determinations of the capillary blood sugar were made. The insulin was administered just before breakfast in doses varying from 20 to 50 units.

The cardiac rate per minute varied from 55 in Case 4111, a male, 46 years of age, to 120 in the case of a 13-year old boy, Case 9769. No striking relationship between the heart rate and the blood sugar values could be seen, probably because no severe insulin reactions occurred. It is notable that in severe insulin hypoglycemia a slow pulse often occurs.

Case 6930, aged 19 years, entered the hospital August 8, 1937, unconscious, in an insulin reaction with a blood sugar of 50 milligrams per 100 c.c. He had taken insulin at 2.00 a.m., risen at 10.30 a.m. in a confused state evidently due to hypoglycemia, taken a second dose of unknown amount and arrived at 2.30 p.m. Even after the injection of 35 c.c. of 50 per cent glucose which raised the blood sugar to 130 milligrams, the pulse rate remained at 62. He fought and struggled with attendants but the pulse remained at 62. However, 30 minutes later, when he suddenly came to normally, the pulse quickly rose to 72. This seemed clearly a bradycardia due to a vagus stimulation associated with the general hypoglycemia effect upon the central nervous system.

The rhythm was slightly irregular in every case except in the three oldest patients, Cases 4568, 14405, and 4111. All younger patients showed a sinus arrhythmia, which was present whether the blood sugar was high or low. Extrasystoles of ventricular origin occurred with some frequency in a girl aged 14 years, Case 14491. The absence of extrasystoles in the remaining curves is notable.

Changes in conduction time were conspicuous by their absence. The P-R interval varied from 0.12 to 0.16 second. In two cases this interval was increased with hypoglycemia and in two cases it was shortened. The Q-R-S time varied from 0.04 to 0.08 second. Slight prolongation was noted in five cases and shortening of the interval in three cases. The S-T time varied from 0.22 second to 0.32 second. In five cases it was slightly prolonged and in three slightly shortened with fall in blood sugar.

The maximal height of the R-wave was found to vary from 5 millimeters in Case 9769, a boy 13 years of age with severe diabetes and a large

TABLE I
Electrocardiograms with Falling Blood Sugar Values

Case No	Sex	Age (yrs)	Dur of DM	Blood Sugar Values			Rate	P R		Q R S		S T		R		T					
				Date	%	Hour		Seconds	Seconds	Max	Lead	I	II	III	V						
																Seconds	Seconds				
13395	F	7	1 2	2-27-36 3-5-36	0.24 0.04	11 55 a m 11 45 a m	90 90	0.12 0.14	0.04 0.05	0.22 0.24	0.24	17 32	V V	2.5 4	4 4.0	1.5 0.5	4 3	T ₂ upright in all Q absent from II at times W form of Q R S in III Depression of S-T in V			
12820	F	9	2 0	2-24-36 2-27-36 3-6-36	0.36 0.28 0.08	12 00 noon 10 20 a m 9 25 a m	80 82 86	0.14 0.14 0.12	0.04 0.04 0.04	0.28 0.28 0.28	0.24	39 28 28	V V V	2 2 3	3 4 4	0.5 1.0 1.0	5 3.5 1.5	T ₂ upright and varies from 4-5 Q R S has W form in Lead III (2) Depressed S-T interval in all leads			
12135	M	9	2 2	2-24-36 2-27-36	0.07 0.18	11 05 a m 9 55 a m	100 105	0.12 0.12	0.05 0.06	0.26 0.26	0.26	24 28	II V	2 2	3 3	0.5 2.0	3 2	T-wave diphasic in V T-wave diphasic in V			
9968	M	9	1 0	3-1-35 3-6-35	0.10 none	11 00 a m taken	68 88	0.12 0.12	0.08 0.06	0.28 0.24	0.28	14 10	II II	3.5 3.5	4 3	0 0	none none	T ₂ flat T ₃ flat Notch in ascending R ₃			
10920	F	10	1 6	3-1-35	0.06	11 20 a m	80	0.14	0.06	0.28	0.28	15	II	1.5	1.0	0.5	none	T ₂ inverted			
9583	M	10	6 8	2-24-36 2-27-36	0.07 0.11	11 10 a m 10 05 a m	88 105	0.18 0.18	0.04 0.04	0.28 0.26	0.26	30 33	V V	1.5 2	2 2	0.5 0.5	2.5 2.0	T ₂ diphasic T ₃ and T ₂ inverted			
13157	M	10	2 1	3-1-35	0.11	11 35 a m	82	0.12	0.04	0.24	0.24	7	I	2.5	1.5	-1.0	none	T ₂ diphasic T ₃ inverted			
11905	M	11	2 9	3-18-36 3-21-36 3-28-36	0.12 0.073 0.08	11 00 a m 11 00 a m 10 10 a m	84 60 67	0.13 0.12 0.14	0.06 0.04 0.06	0.32 0.28 0.28	0.28	22 21 19	V V V	3.5 2.5 3.5	4 5 5	0 2.0 0.5	2 1 2	(1) Rhythm irregular Q-R S has W form in III T ₂ flat T ₂ upright and diphasic P ₂ inverted (2) T ₂ upright P ₂ inverted Q R S has W form (3) P ₂ inverted T ₂ upright and diphasic			
14386	F	11	0 1	2-24-36 2-27-36	0.08 0.15	11 50 a m 9 55 a m	67 82	0.16 0.14	0.04 0.04	0.26 0.26	0.26	15 24	V V	1.3 1.5	1.0 1.0	-0.3 -0.3	2 2	T ₂ inverted T ₃ upright T ₂ upright Depression of S-T ₃ interval			
6113	M	11	8 5	2-24-36 2-27-36 6-12-36	0.08 0.08 0.11	12 50 noon 9 30 a m 11 15 a m	97 87 83	0.16 0.16 0.18	0.06 0.06 0.08	0.26 0.26 0.28	0.26	38 34 25	V V V	4.5 3.5 4.0	3.0 4.0 3.5	-2.0 -1.0 -0.2	-1.0 3.0 1.5	T ₂ inverted T ₂ upright P ₂ inverted T ₃ inverted T ₂ upright			
12190	M	12	9 0	3-5-36 3-6-36	0.07 0.07	11 30 a m 9 40 a m	85 80	0.16 0.16	0.04 0.04	0.26 0.28	0.26	34 25	V V	2.0 2.0	2.5 3.0	1.0 1.0	2.0 2.0				

TABLE I—Continued

Case No	Sex	Age (yrs)	Dur of DM	Blood Sugar Values			Rate	P R		Q R-S	S T	R		T				
				Date	%	Hour		Seconds	Lead	Max	I	II	III	V				
															Seconds	Seconds		
																	Seconds	Seconds
4830	M	13	11 3	3 1-36	0.07	11 20 a m	78	0.16	0.05	0.24	15	II	2.0	1.5	1.0	none	W form of Q-R S in III W form of Q R-S in III	
9769	M	13	9 7	3 1-35 3 6 35	0.06 0.39	11 40 a m fasting	120 120	0.12 0.12	0.04 0.04	0.24 0.22	5 64	II I	1.5 1.5	1.5 1.5	0.3 0.3	none none		
14191	F	14	0 0	3 24-36 3 26 36	0.06 0.14	11 00 a m 9 40 a m	95 90	0.14 0.14	0.06 0.04	0.26 0.26	13 22	II V	1.0 1.0	2.0 2.0	0.5 0.5	2.0 0.5		Rhythm regular but for 3 extrasystoles Extra ventricular systole
8546	F	15	6 5	2-27-36 3- 5 36	0.34 0.06	4 30 p m 11 30 a m	80 60	0.18 0.16	0.04 0.04	0.30 0.30	12 14	II II	2.5 3.5	3.0 3.0	1.0 0.5	-0.5	1.0	Notching in descending R ₃ SI slurring descending R ₂ and R ₃
1715	F	15	6 7	2-24-36 2 27 36	0.06 0.06	11 00 a m 9 20 a m	70 81	0.15 0.15	0.04 0.06	0.28 0.28	11 13	I V	3.0 3.0	3.0 3.0	-1.5 -0.5	5 5	T ₃ inverted T ₃ inverted	
10778	M	15	9 1	2 24-36 2 27 36	0.19 0.13	11 35 a m 9 50 a m	90 118	0.12 0.12	0.04 0.06	0.26 0.26	26 33	V V	2.5 2.0	2.0 +1.0	-2.0 -1.5	1.0 1.0	1.0	Inverted P and Q-R-S T in III Upright T ₃
1568	F	25	11 2	3-17-36 3 24-36	0.39 0.14	fasting 11 00 a m	90 78	0.16 0.14	0.06 0.08	0.24 0.28	10 10	I I	2.0 2.0	1.0 1.5	-1.0 -1.0	Flat Flat	Flat	Inversion of all complexes in III Inverted P ₃ Notching of R ₂ and slurring R
14105	F	30	7 1	3 24-36	0.04	11 00 a m	60	0.16	0.04	0.32	14	V	1.0	1.5	0.5	1.5	Q ₁ inverted T ₃ upright P ₃ and inverted	
4111	M	46	14 6	3 14-36 3 20 36	0.062 0.20	12 noon 11 00 a m	64 55	0.18 0.16	0.08 0.06	0.34 0.30	13 22	V V	2.5 2.0	2.0 3.0	0.5 1.0	3.5 5.0	T ₃ inverted R ₃ low notched T ₃ inverted R ₃ low notched	
12125	M	7	2 6	3 6 36	0.05	9 30 a m	100	0.14	0.06	0.22	16	V	2.5	2.0	Flat	4.5	Upright T ₃	
12852	M	10	2 4	7 7-36 7- 7-36	0.21 0.28	9 45 a m 11 45 a m	83 73	0.14 0.14	0.06 0.06	0.28 0.26	7 7	II II	3 4	3.5 4.0	Flat Flat	1 1	1	W form complex in III P ₃ inverted T ₃ shallow depression in both
7878	M	11	9 2	7- 7-36 7- 7-36	0.26 0.08	9 20 a m 12 10 noon	91 81	0.14 0.14	0.06 0.06	0.24 0.24	11 16	V V	1.5 2.0	2.5 3.0	0.3 -0.5	1.5 1.5	T ₃ upright	
8156	F	15	7 0	7- 6 36 7- 7-36	0.17 0.08	9 45 a m 11 35 a m	91 91	0.12 0.12	0.06 0.06	0.28 0.28	9 10	I I	2.0 1.5	1.5 1.0	Flat -0.5	1.0 1.5	1.0	Inversion of complexes in III T ₃ upright Inversion of complexes in III T ₃ upright
14478	F	16	8 0	7 7-36 7- 7-36	0.19 0.12	10 10 a m 11 53 a m	78 70	0.14 0.11	0.06 0.04	0.28 0.32	9.5 9.0	II II	1.0 1.0	0.5 1.0	Flat Flat	0.5 Flat	0.5	SI notching in R ₃ Inverted P ₃ SI notching in R ₃ Inverted P ₃
1804	M	19	11 0	7- 6 36 7- 7-36	0.26 0.13	9 50 a m 12 noon	80 73	0.16 0.16	0.06 0.06	0.28 0.28	11 12	V V	2 2	2 1.5	-0.5 -0.5	4 6	4	Inverted P ₃ and P ₆ Inverted P ₃ and P ₆

liver, to 38 millimeters in a boy 11 years of age, Case 6113, also a severe case of long duration. The R-wave was maximal in the fifth lead in 30 records, in the second lead in 13 records and in the first lead in 7 records. Changes in the elevation of the R-wave occurred with changes in the blood sugar in a few instances. In four cases, with the fall of the blood sugar during the action of the insulin, the elevation of the R-wave increased, and in five it was diminished.

The deflection of the Q-wave was measured in four leads. Q-waves were absent in at least one lead in all patients, with two exceptions. Very deep Q-waves were observed in three records of Case 6113, a boy of 11 years, with diabetes of long duration. In Lead V the Q-waves were often of great depth, varying from 0 to 28 millimeters.

The T-waves were upright in all cases in the first two leads. There were no striking changes in the T-wave in the first lead. In the second lead, four cases showed a deflection of 1 millimeter or less in the second lead, T-wave. The T-wave in the third lead was flat in five cases and inverted in nine cases. With a fall in the blood sugar, there was a fall in the height of the T-wave in nine cases, but in three the T-wave increased in amplitude while the blood sugar fell. In eight cases there was no change in the T-wave with a change in the blood sugar.

The T-waves in the fifth lead were upright in 10 cases and flat in two cases. With a falling blood sugar due to insulin, there was a lowering of the T-wave in this lead in five cases, in six cases, no change occurred and in two cases the T-wave rose with the falling blood sugar.

W-forms of the Q-R-S intervals occurred in a number of cases as well as inversion of the T-wave or of the entire complex in the third lead.

Miscellaneous changes may be noted. In Case 13395, a girl seven years of age, as the blood sugar fell a more marked depression of the S-T interval in the fifth lead occurred. The T-wave was upright in all four leads. In Case 11905 a variation in the form of the complexes occurred. The early leads were characterized by a lower R-wave and a higher T-wave than later leads. At this time the blood sugar level was 0.07 per cent. Also, in this curve the T-wave in the third lead varied somewhat, being slightly inverted or diphasic in certain cycles. A slightly depressed S-T interval was noted in Case 12190, while the blood sugar was 0.07 per cent and especially in Case 8156, a girl 15 years of age with severe diabetes. Slight notching in the R-wave of the second lead with slurring of the R-wave in the fifth lead occurred in the record of Case 4568, a girl 25 years of age with uncontrolled diabetes of 14 years' duration.

In summary, it may be said that the electrocardiographic changes noted in these cases are slight and not clearly correlated with the intensity of insulin action as indicated by variations in the blood sugar. This lack of correlation is intensified if one compares the mild degrees of hypoglycemia in this series with the severe and prolonged hypoglycemia of the series

reported by Hadorn¹ and de Chatel and Palisa² Actually the blood may contain no glucose without symptoms therefrom as reported in the review by Marble¹⁴

ABSENCE OF CARDIAC PATHOLOGY IN FATAL HYPOGLYCEMIA

The effect of a fatal dose of insulin is illustrated in the following case report

CASE REPORT

Miss D, Case 12882, aged 27 years, had been treated with insulin since the onset of diabetes in 1928 On August 9, 1934, she returned to her home from work, behaved queerly, and rapidly became unconscious During the next 12 hours, 200 units of insulin were given and she had convulsions At noon on August 10 she was unconscious and cyanotic with irregular gasping respiration, and immediately 40 c c of 50 per cent glucose solution were given intravenously Respiration became regular, cyanosis disappeared and the pulse rate, at first 144, fell almost to normal, but at no time did she regain consciousness Her muscles were at times in tonic contraction and there was a suggestion of the opisthotonus position A double Babinski sign was present The pupils were dilated All normal tendon reflexes were somewhat exaggerated Lumbar puncture showed clear fluid with a pressure of 650 mm, a trace of globulin, 30 cells, no sugar was present The analysis of the spinal fluid was carried out at the New England Deaconess Hospital, using a slight adaptation of the Folin technic for blood sugar determination Laboratory blood sugar analyses were as follows

Date	Time	Blood Sugar (%)
August—1934		
10	8 00 a m	Too low to read
10	10 30 a m	Too low to read
10	12 30 p m	Too low to read
10	3 30 p m	27 mg in 100 c c
11	7 00 a m	500 mg in 100 c c
	at autopsy	540 mg in 100 c c

TREATMENT

She received during 18 hours, 600 grams of glucose in solution intravenously or under the skin At first it was given in 50 per cent solution, 40 c c at a time Later a cannula was tied into a vein and glucose solution continuously administered Adrenalin did not help

During the first 20 hours, no urine was obtained At the end of this time, 3 ounces were obtained by catheter in which the chloride concentration was 0.2 gram per 100 c c During the last 12 hours of her life, the blood sugar was high, and the urine contained much sugar Bladder urine at autopsy contained 6.8 per cent sugar She never regained consciousness and died 39 hours after onset of hypoglycemic symptoms

Pathologic Report The gross appearance of the brain as well as of all other tissues was normal, except for slight edema possibly due to the prolonged administration of glucose solution

Microscopical examination was negative except for the tissues described below

Heart Slight edema and some perivascular fibrosis

Lung Congestion and some edema Rare polymorphonuclear leukocytes, in alveolar walls together with mononuclear leukocytes in alveoli

Spleen Moderate congestion

Pancreas Acinar and duct tissue negative Islands reduced in number and in size One or two show hypertrophy of so-called "cobra" type

Liver Moderate central congestion Glycogenic vacuolization of a few nuclei in periportal hepatic cells

Adrenal Moderate lymphocytic infiltration of medulla Usual distribution of lipid in cortex

Kidney Moderate congestion No evidence of glycogenic vacuolization

Aorta Some swelling of subintimal ground substance with early lipid deposition Few mononuclear phagocytes present, many of which contain considerable amounts of lipid, others of which apparently had been migrating

Brain Slight subpial and perivascular edema Pons negative Cerebellum negative

DISCUSSION

Electrocardiographic Changes The youthful diabetics of this series receiving small doses of insulin without any serious clinical evidences of hypoglycemia, show some electrocardiographic changes, but these changes are slight, inconstant and of little consequence

In agreement with our findings are those reported by Hadorn¹ and by de Chatel and Palisa² in two series of patients studied during the severe prolonged hypoglycemic states produced by insulin in treating schizophrenia

(1) Hadorn had an opportunity to make 47 observations upon 31 patients undergoing the hypoglycemia treatment for schizophrenia. At the lowest levels, the blood sugar values reached were under 20 milligrams per 100 c.c. His patients were all between the ages of 20 and 40 years with the exception of five whose ages were from 43 to 54 years. The insulin injections were given intramuscularly, the dose varying between 10 and 200 units. He had no cases of initial hyperglycemia. In 21 of Hadorn's cases the pulse rate increased to 100 and in 11 cases it became slowed to 50. In 10 cases there was no change in the pulse rate. The pulse rate did not seem to run parallel to the degree of lowering of the blood sugar. Often, the increase in heart rate occurred shortly after the insulin injection and not at the time of the hypoglycemia. Many times it also occurred that the increased heart rate did not develop until after the noon-day meal or even after the evening meal. In one case, the tachycardia lasted for several weeks. In a majority of Hadorn's cases slight increase in systolic blood pressure occurred, 10 to 20 millimeters, and usually the diastolic pressure fell. In three experiments the blood pressure rose to levels of 170 to 180. Only exceptionally did disturbances of the rhythm occur. The changes observed by Hadorn in the electrocardiograms of his patients may be summarized as follows:

1 The T-wave was inverted once and the P-R interval became shorter in the cases where the pulse rate rose. In 18 cases the P-Q interval was increased by 1/100 to 1/200 of a second and in eight cases it was shortened. The Q-R-S complex was unchanged in 22 cases, was shortened in six and lengthened by 1/100 second to 3/100 in three cases.

2 The S-T interval was unchanged in 26 cases and in 16 cases there was a depression of the S-T interval. The frequency of this depression of the S-T interval is in contrast to the findings of de Chatel.²

3 In only 10 cases was the T-wave unchanged. In 32 cases there was more or less marked lowering of the T-wave.

4 The Q-T interval was lengthened in 32 cases. In six cases a U-wave or a doubling of the T-wave occurred.

The observations made by de Chatel and Palisa² were in a series of cases of severe induced hypoglycemia, often with coma and convulsions. In these states the

authors noted occasionally a flattening and a lowering of the T-wave, a broadening of the Q-R-S complex and appearance of a sinus arrhythmia, various extrasystoles, auricular fibrillation, prolongation of the conduction time. Against the theory of glycogen impoverishment is that rabbits' heart muscles even with great doses of insulin do not become more glycogen poor. Further, the electrocardiographic changes are not relieved by the administration of grape sugar and, finally, that they do not appear with spontaneous hypoglycemia. However, certain cases, even after the largest insulin doses, show no electrocardiographic changes in the severest types of hypoglycemic shock, and the others may show only a lowering of the T-wave. As a rule, the changes develop within 45 minutes and last for half an hour to an hour after the cessation of the unconsciousness. They were all quite similar and consisted in the lowering of the T-wave. The thoracic lead from the back to the precordium is exceptionally sensitive and at times shows a complete reversal of the T-wave after insulin whereas de Chatel and Palisa did not observe this phenomenon either in the first, second or third leads. In two of their 19 cases there was a sinus arrhythmia. The changes stand in no quantitative relation with the severity of the insulin shock. Patients who appear restful and cheerful an hour after the insulin injection show the same changes as later when in deep coma with profuse sweating, or finally, up to within 15 minutes after the breaking off of the attack. Some cases, even in deep coma with a low blood sugar, show no electrocardiographic changes whatsoever. They gave their insulin intramuscularly whereas in earlier tests without exception the insulin had been given intravenously.

Possibly the absorption from the muscle tissue might lead to certain changes in the insulin which do not allow so direct an influence upon the heart muscle as if the insulin were given intravenously. They are confident it does not depend on the purity of the insulin because they obtained the changes when insulin first began to be manufactured and they were the same as at present when it is much purer.

Their practical conclusions were

- 1 That insulin does not exert on the healthy heart the anticipated harmful action which in general has been accepted, even with very low values of the blood sugar, a normal electrocardiogram could be obtained,

- 2 That their electrocardiographic studies show that even after months of induced severe hypoglycemic attacks permanent changes are not observable,

- 3 That all of their observations relate exclusively to patients with completely healthy heart muscle, and they cannot be considered as contradicting in any way results obtained in coronary disease after the administration of insulin.

In 50 per cent of Hadorn's cases, increase in the heart rate occurred and indeed often before the beginning of the hypoglycemia. In general, the view has been held that insulin is a parasympathetic stimulant. There is a difference of opinion on this score. A toxic dose of insulin acts through the central sympathetic chain to produce an out-pouring of adrenalin and so leads to a primary tachycardia. Even before hypoglycemia has occurred, a toxic insulin dose could, therefore, paralyze the vagus even though small doses of insulin might be stimulating. The tachycardias in Hadorn's group seemed to be due to adrenalin stimulation.

Smaller insulin doses may act as vagotropic drugs and may thus bring about the bradycardia which has frequently been observed. No increase in the work of the heart occurs when insulin slows the heart. Indeed, Bodo¹² as well as Visscher and Muller¹³ demonstrated with the Starling heart-lung preparation, that insulin had a tonic effect upon the heart, in-

creasing the power of the cardiac fibers without any increase in energy liberation

In cases where no change in pulse rate has occurred, we have positive and negative compensating chronotropic properties of insulin. That adrenalin is in some cases called forth by insulin is indicated by the fact that the systolic blood pressure rises while the diastolic blood pressure falls, a characteristic of adrenalin action. Secondly, leukopenia with a later increase in the leukocytes has occurred. One author holds that it is not the fall in the blood sugar which determined the symptoms of insulin shock but the strength of the opposing reaction from the adrenalin. Thus, the pounding of the heart, the tremor, and the pressure under the sternum are adrenalin symptoms whereas the hunger, weakness, sweating are the direct results of the hypoglycemia. The blood sugar level may fall to 40 milligrams after 5 units of insulin and yet no symptoms result whereas if it reached the same level with a dose of 40 units the symptoms may be marked. It is noteworthy that our children had practically no symptoms even with blood sugar values as low as 0.04 (40 milligrams) per cent.

A rise in blood pressure occurs only when the blood sugar falls below 60 milligrams, according to one author, but LaBarre and Houssa³ found that, in animals when the blood sugar fell under 95 milligrams the blood pressure rose due to the secretion of adrenalin.

Clinical Changes Unfavorable effects of insulin have been noted almost exclusively in hearts damaged by coronary disease. Thus, Schonbrunner⁴ described a 73 year old diabetic woman with a low Q_s , in whose electrocardiogram there developed regularly 15 minutes after insulin a negative inversion of the T-waves without simultaneous hypoglycemia. In 1923 at the New England Deaconess Hospital a man who had had angina pectoris for many years, died during the night 11 hours after receiving a dose of only 3 units of insulin. At autopsy, his heart had advanced coronary disease with old areas of infarction. At that time, when insulin was new, the possibility of its having precipitated this fatal attack required frank statement. Gigon,⁵ as well as others, has described diabetic patients with severe coronary disease who have died suddenly shortly after receiving insulin. As years have passed, the favorable effects of insulin have become more apparent. The following table shows that diabetics, with fatal coronary disease, live longer, the longer insulin was used.

TABLE II
Diabetics with Coronary Disease
The Advancing Age at Death During the Insulin Era

	1923-1926	1927-1929	1930-1932	1933-1935
Average Age at Death	60.9	62.7	64.4	68.2
Average Duration of Diabetes	11	13	13	15
Number of Cases	55	56	94	58

ANIMAL EXPERIMENTS

In animals negative T-waves have been noted in the electrocardiogram after a dose of insulin as well as changes in the heart rate and in the blood pressure. A direct toxic effect has been described affecting stimulus formation, stimulus conduction, and contractility of the heart muscle during a period of hypoglycemia due to insulin. It has been pointed out, however, that the variation in the T-waves and the level of the blood sugars are not parallel.

Rabbits, when given insulin and killed during hypoglycemia, showed about the same glycogen content as control animals. Both with intramuscular and intravenous injection of insulin they found T-wave depression in the animals. With very small doses of insulin (4 units) Hadorn¹ observed an increase in the height of the T-wave. In one case, however, the blood sugar fell to 21 milligrams without a T-wave change. In one animal, the blood sugar rose after 20 units of insulin and during this period they found an isoelectric T-wave. S-T depression did not occur in his animals. Lengthening of the Q-T interval occurred in the animals. With adrenalin injection into the animals, they show typical depressions of the T-wave, negative T-waves and often these were of the coronary type.

Milles and Smith⁶ injected epinephrine into the saphenous vein and the coronary artery and observed electrocardiographic changes. A reduction in the amplitude of the T-waves was found as well as other changes of the T-wave and actual inversion. Deviation of the S-T interval from the isoelectric line occurred as well as extrasystoles and actual ventricular fibrillation.

Douglas, Gelfand, and Shookhoff⁷ found that the injection of epinephrine into the muscles of the cat would produce marked displacement of the S-T segment in the electrocardiogram. These S-T changes were abolished by nitroglycerine, and were therefore attributed to coronary spasm. Milles and Smith⁶ attributed the changes caused by epinephrine to an increase of the myocardial requirements for oxygen beyond the available supply, with consequent functional anoxemia of the myocardium.

Soskin, Katz and Frisch⁸ produced hypoglycemia in animals in various ways and concluded that insulin exerts a specially harmful effect upon the heart regardless of hypoglycemia, a point of view difficult to understand when one remembers that insulin is a natural hormone produced physiologically throughout life.

In summary, the important thing is the question of the T-wave. The changes observed are of short duration, and may be reproduced by injection of adrenalin. Many factors such as anemia, CO poisoning, oxygen lack, general infections as well as digitalis itself cause temporary changes in the T-wave. At present, the balance of evidence indicates that the electrocardiographic changes following insulin injections are probably secondary adrenalin effects and without serious significance, except in the presence of coronary arteriosclerosis.

INSULIN AND CARDIAC METABOLISM

The effect of insulin upon the respiratory quotient, oxygen consumption in hyperglycemia and in hypoglycemia, glycogen deposit and changes in cardiac muscle during insulin action have been repeatedly studied and the results recently reviewed by Cruickshank⁹. In the isolated heart, in the presence of hyperglycemia, insulin increased the oxidation of sugar and the deposition of glucose as glycogen. When hypoglycemia of severe grade was produced, ordinarily the cardiac glycogen reserve is drawn upon. If the hypoglycemia persists, then the heart utilizes other sources of energy and can survive with no sugar in the blood. During the hypoglycemia the addition of insulin has a protective effect in that even then it causes the deposition of glycogen in the heart muscle.

Using diabetic dogs with experimental coronary occlusions, Himwich, Goldfarb and Nahum¹⁰ studied the cardiac metabolism and found data supporting the use of insulin and glucose. They studied 34 animals. They concluded that the infarcted area lost appreciable quantities of the glycogen which appeared in part as increased amounts of available carbohydrate and of lactic acid. Although the normal heart usually absorbs lactic acid from the blood, after occlusion the heart was found to pour lactic acid into the blood stream, probably due to the reduced oxygen supply to the infarcted area. Glucose was absorbed from the blood both before and after the coronary occlusion. These data again suggest that in diabetic patients, especially, the use of glucose and insulin may be of real value in cases with coronary occlusion. Furthermore, Himwich, Goldfarb and Fazikas¹¹ found that the heart muscle oxidizes non-fatty substances, that is, carbohydrates, very well.

Actually it must be remembered that the results of insulin hypoglycemia are chiefly dependent upon the degree to which sugar is lost from the blood and the length of time the tissues are without a supply of glucose from the blood. Certain tissues, like the liver, have a store of glucose upon which they can surely subsist. Other tissues, like the central nervous system, can withstand serious hypoglycemia for only a comparatively short time without the development of irreversible changes.

SUMMARY

1. Electrocardiograms in 25 young diabetics and the record of a fatal case of insulin hypoglycemia are reported.

2. Insulin hypoglycemia has no serious effect upon the normal diabetic heart. Bradycardia is as common as tachycardia.

3. Insulin hypoglycemia may, by reason of its accompanying stimulation of adrenalin secretion, have serious effects upon the heart damaged by coronary disease.

4. Insulin hypoglycemia of sufficient duration will cause irreversible changes in the central nervous system and death.

5 The proper use of insulin and diet in coronary disease complicating diabetes prolongs life

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UNILATERAL HEMOGLOBINURIA ITS OCCURRENCE IN INFARCTION OF THE KIDNEY*

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HEMOGLOBINURIA is regarded as symptomatic of hemoglobinemia. A small amount of hemoglobin may be free in the blood plasma without appearing in the urine, being taken up and converted to bilirubin by the reticulo-endothelial cells. But the renal threshold for hemoglobin is apparently very low, so that hemoglobinuria is a fairly delicate indicator of hemoglobinemia. Contrary to hemoglobinuria, hematuria is practically always due to a local disorder of the kidneys or urinary passages, though in the so-called essential hematurias the anatomic substratum may be difficult to discover.

In the present note we desire to record briefly three observations showing that this distinction between the significance of hemoglobinuria and that of hematuria, while true in the vast majority of cases, does not invariably hold, occasionally, hemoglobinuria is due to a lesion of the kidney and is then unilateral if the renal affection is one-sided. A few instances of hemoglobinuria caused by renal disease are recorded in the literature. Thus, Bittorf¹ reports three cases of acute glomerulo-nephritis which, after apparently having been cleared up for months, underwent recurrences associated with hemoglobinuria. In each instance the hemoglobinuria appeared after exposure to cold. Since there was no evidence of hemolysis in the blood of an arm vein, the hemoglobin must have been freed in the kidney. He also states that he observed hemoglobinuria, in addition to hematuria, in a case of subacute bacterial endocarditis with embolic focal nephritis. Wagner² and Senator³ also mention hemoglobinuria in the course of acute or chronic Bright's disease. Our observations concern three instances of infarction of the kidney occurring in heart disease.

CASE REPORTS

Case 1 This patient was seen by one of us (E L) in consultation in 1919. She was a woman of 55 years who had suffered from mitral stenosis with auricular fibrillation for a number of years. She was suddenly seized with severe, cramp-like pain in the right side of the abdomen. Ovarian or appendicular disease was suspected. The urine at this time did not contain blood. Soon, however, the pain shifted to the left upper abdomen and the left kidney became palpable and tender. The leukocyte count was 32,000 with 82 per cent polymorphonuclears. The bladder urine was acid, contained albumin, a few erythrocytes, and some hyaline and granular casts. Roentgen-ray examination was negative for calculus. Cystoscopy was performed by

* Received for publication September 23, 1937

Dr Leo Buerger The urine from the right kidney was of normal color and contained albumin and casts and a few erythrocytes but not hemoglobin The urine from the left side was red and gave a positive guaiac reaction, but no erythrocytes were to be found in the sediment From the pelvis a large amount of old blood was evacuated The hemoglobinuria persisted for several days It then cleared up, as did the abdominal symptoms There was no recurrence of similar symptoms

Case 2 A woman of 30 years had had rheumatic heart disease since childhood She presented the classical signs of mitral stenosis On February 17, 1925 at 12 30 a m, when feeling comparatively well, she was suddenly seized with severe abdominal cramps, particularly in the right lower quadrant The pains lasted all night and were not relieved by repeated injections of codein Unfortunately the urine was not observed during the night

A specimen of urine obtained at 10 a m was acid and intensely red Very few erythrocytes were found in the sediment after centrifugalization, although numerous hyaline and granular casts were present The guaiac test was positive The protein content was 0 31 per cent

February 18, the urine was very red The sediment after centrifugalization contained very few erythrocytes, but numerous leukocytes and some hyaline and granular casts were present The protein content was the same as before The guaiac test was positive

February 19, the morning urine was still very red The guaiac test was positive The sediment after centrifugalization contained no erythrocytes but numerous granular casts

The evening urine was also very red and gave a positive guaiac reaction In the sediment only isolated erythrocytes were seen, and also a few casts and some polymorphonuclear leukocytes Some of the casts were stained golden by hemoglobin Large clumps of hemoglobin were present

Daily examination of the urine from February 20 to 23 revealed continuance of the hemoglobinuria in the absence of hematuria The hemoglobinuria disappeared on February 24 and did not return

During the first two days the right kidney (which was ptosed and readily palpable) was very tender, it was not notably enlarged The tenderness rapidly passed away, and the patient remained with only the symptoms of the preexisting heart failure It is of interest to note that one day after the infarction occurred, examination of the blood revealed 29,600 leukocytes per cubic millimeter, 94 per cent of which were polymorphonuclears

Case 3 A woman of 36 years was under observation because of orthopnea and swelling of the feet dating back to the last weeks of a pregnancy which had terminated five months earlier In a pregnancy 16 years before she had suffered from a pyelitis On admission to The Mount Sinai Hospital on February 18, 1936, the patient was cyanotic and orthopneic She had cardiac enlargement, tachycardia, and gallop rhythm There was engorgement of the lungs and liver and edema of the feet The blood pressure in the left arm was 170 systolic and 130 diastolic The pulsations in the right upper extremity were small and the oscillometric excursions diminished The urine was acid and contained a large amount of protein and scattered erythrocytes and leukocytes Although the urea nitrogen content of the blood was only 17 mg per cent, the concentration test revealed severe impairment of renal function, the maximum specific gravity was only 1 012 The roentgenogram revealed a calculus in the right kidney It was thought that the patient's symptoms were due to heart failure secondary to hypertension and perhaps coronary artery disease Whether the hypertension was essential in type or the result of a pyelonephritic contracted kidney was not clear

February 27, the patient was suddenly seized with severe knife-like pain in the left upper quadrant which persisted for about an hour The skin was cold and

clammy The pulse was feeble and rapid, the blood pressure unobtainable The urine was yellow in color In the sediment of the centrifuged urine, there were 100 to 200 leukocytes and 10 to 20 erythrocytes per high power field

February 28, she complained of left costovertebral pain radiating to the right upper quadrant There was shock tenderness in the left costovertebral region The temperature rose to 101° There was a leukocytosis of 21,000 with 76 per cent polymorphonuclears* Later in the day, the left kidney became palpable and tender The urine was unchanged in color There was no increase in the small number of erythrocytes found in the sediment of the centrifuged urine At this time, the nature of the attack was obscure, the most likely possibilities seemed to be left-sided renal colic of calculous origin (there was known to be a stone in the right kidney) or infarction of the left kidney

February 29, a specimen of urine was obtained which was burgundy red in color On centrifuging, there was a small amount of white sediment, but the supernatant fluid remained red and gave a very strongly positive guaiac reaction Spectroscopic examination of the supernatant fluid disclosed oxyhemoglobin in solution The sediment contained a moderate number of leukocytes, some of which were clumped, a few hyaline and granular casts, and about 20 erythrocytes per high power field On the basis of the hemoglobinuria, a diagnosis of infarction of the left kidney was made

From February 29 to March 2, inclusive, the burgundy red color of the urine due to the presence of dissolved hemoglobin persisted The sediment of the centrifuged urine contained between 1 and 6 erythrocytes per high power field The urine obtained on the morning of March 3, the day of death, was yellowish in color but still gave a strongly positive guaiac reaction

Necropsy revealed recent thrombosis of the right circumflex coronary artery and old occlusion of the left anterior descending branch of the left coronary artery There was myofibrosis of the anterior and posterior walls of the left ventricle with an aneurysm of the posterior wall Over areas of fresh myomalacia at the apices of the left and right ventricles were mural thrombi There was embolic occlusion of the left renal and superior mesenteric arteries The left renal artery, just beyond its origin, was occluded by a recent blood clot The left kidney was infarcted in toto, and was largely a dirty brown red in color The right kidney was the seat of pyelonephritic contraction

COMMENT

It is not immediately obvious why hemoglobinuria should occur in some instances of renal infarction while the large majority present hematuria The arteries of the kidney are typical end arteries in the sense of Cohnheim and renal infarcts are probably always anemic in their inception The gray-colored anemic area is usually surrounded by a red border of circulatory stasis and collateral hyperemia, with hemorrhages from dilated capillaries Microscopic examination of this portion shows the tubules filled with blood coming from the ectatic and ruptured intertubular capillaries This is the source of the *hematuria* which commonly occurs in infarcts Hemoglobinuria, however, when it occurs, is probably to be accounted for by a different mechanism Following the infarction, sufficient blood may reach the infarcted area to make it hemorrhagic In the autolysis which the infarcted area undergoes, large numbers of erythrocytes are destroyed with liberation of their hemoglobin Diffusion of the free blood pigment into neighboring

* High leukocytosis is not at all uncommon in infarction in any organ, it may also occur, as one of us⁴ has pointed out, in intracardiac thrombosis not followed by infarction

patent uriniferous tubules would cause hemoglobinuria. Evidence of such diffusion is found in hemosiderin deposits in the vicinity of old hemorrhagic infarcts. Because of the presence of old blood in the renal pelvis in the first case, the question must be brought up of the possibility of some hemolysis occurring there. It is to be noted that in Case 3, which came to postmortem examination, there was no old blood in the pelvis.

From the above observations, it is evident that hemoglobinuria is not absolutely pathognomonic of hemoglobinemia, for it occurs in connection with embolic infarction of the kidney. In our first case, the clinical picture was that of renal infarction and the hemoglobinuria was proved to be purely unilateral. In Cases 2 and 3 the clinical picture was the same as in Case 1. In Case 3 unilateral infarction was demonstrated at the postmortem examination. There is no reason to doubt that, although ureteral catheterization was not carried out in these two cases, the hemoglobinuria was also unilateral.

Judging by the third case, the phenomenon may well prove to be occasionally of practical diagnostic significance in the differentiation of infarction of the kidney from nephrolithiasis occurring in a patient suffering from cardiac disease. It is evident that studies should be made of separated specimens of urine, by means of ureteral catheterization, in cases of hemoglobinuria, particularly those in which the condition is not manifestly hemoglobinemic in origin.

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THE PRESENT MORTALITY OF DIABETIC CHILDREN—A REMEDIABLE AND THEREFORE HOPEFUL INDEX OF THE FUTURE OF THE DIABETIC CHILD*

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WHEN a diabetic child dies today it causes me far more pain than half a generation ago. Before the discovery of insulin we did not expect diabetic children to live and if they did, we knew their existence would be much "labor and sorrow" as for people passing three score years and then until diabetic coma almost mercifully snatched them away. At that time diabetic children seldom survived a year, but in each quinquennium the duration of the fatal cases has nearly doubled, to 2.7 years for 1927, to 4.7 years for 1927-1932, to 9 years for 1932-1937. Today the situation is sharply altered. My own cases show a present mortality of about one per hundred per year, and calculations of the Metropolitan Life Insurance Company based upon the same group indicate that the life expectancy of the diabetic child of 10 years is 31.7 years. I know too that it is possible for a large part of these years to be spent happily and productively. Therefore, for diabetic children to die during the first or second decade of diabetes is truly deplorable.

Diabetic Coma. Until the use of insulin, diabetic coma came as a bolt from the night and took practically all children. But since we have had insulin you and I know that the death of a single child from diabetic coma signifies pure and unadulterated neglect and nothing else. Groping in the darkness we all were prior to insulin, we had reached the stage, nevertheless, that in hospitals coma had almost ceased to originate *suu genens*. When I arrived we soon learned that even in actual coma it was the child with the best odds who had the best prognosis. In our series treated during coma at the New England Deaconess Hospital there has been 1 death in 83 children under 15 years of age and 3 deaths among 129 patients in coma between 15 and 20 years. At the Children's Hospital in Boston I am told by Dr. Butler that there has been no death in the institution from diabetes of any cause in the last 15 years. Contrast these facts with the report of the New York State Department of Health that in 1935 there were 107 deaths of the deaths of my diabetic patients with onset in childhood at the age of 15 years since I gave my first dose of insulin on August 7, 1911.

My diabetic children, and I use the word children in the fatherly sense, for once a child always a child to a parent, have numbered 1071 † be-

* Received for publication August 12, 1937

† One hundred sixty-one children died before insulin was used in this clinic, August 1922

TABLE I

Fatal Results During 15 Years Treatment of 1063 Diabetic Children

August 1922-1937

The Causes of Death of 104 Diabetic Children

Date	Deaths Coma		Deaths Non-coma									
			Tuber- culosis		Infec- tions		Hypo- glycemia		Acci- dents		Misc	
	No	Per Cent	No	Per Cent	No	Per Cent	No	Per Cent	No	Per Cent	No	Per Cent
1922-1927 Total 35 Av Dur 2 7 yr	32	91	0	0	3	9	0	0	0	0	0	0
1927-1932 Total 27 Av Dur 4 7 yr	19	70	2	7	3	11	2	8	1	4	0	0
1932-1937 Total 42 Av Dur 9 yr	18	43	7	17	11	26	2	5	1	2	3	7

August 7, 1922 and July 1, 1937 Of these, now scattered literally all over the world, there have come to my attention the deaths of one hundred and four It is possible there are a very few more, because the complete "follow-up" was over six months ago Among the causes of death diabetic coma is foremost and despite the relative innocuousness of this complication in childhood at the Children's Hospital and the Deaconess Hospital, just cited, in the first five-year period 1922-1927, 91 per cent of the 35 deaths were attributed to it In the second five years coma deaths fell to 70 per cent among the 27 deaths, and even in the five years ending now it has caused 43 per cent of the 42 fatalities This is actually higher than the coma mortality for all my patients of all ages in the eight years prior to insulin when it was only 41.6 per cent Yet you and I believe a death from diabetic coma to be needless and almost as inexcusable as a death from diphtheria

What can one do about it? We can reiterate the necessity for insulin both to doctor and patient in season and out of season, and of enough insulin whenever glycosuria exists, particularly in the presence of infections or complications of any sort and we can emphasize attention to the rules I have so often given patients

A Never omit insulin unless the urine is sugar free Keep to your diet and in case of an infection take more insulin if necessary to keep sugar free It is imperative to test the urine frequently during an acute illness

B If you feel sick and especially if you have FEVER, NAUSEA and VOMIT-

ING or even severe pains in the abdomen 1 Call a doctor 2 Go to bed 3 Take a cup of coffee, tea, cocoa shells or broth every hour and live upon acute illness diet (oranges 3, oatmeal, small portion, bread, 3 slices, milk, one quart, 1 egg, little butter) If the urine contains sugar, take regular insulin every hour under your doctor's direction 4 You need the entire time of a nurse or friend to care for you until you are well 5 Move the bowels with an enema

Should we teach a test for acetone or diacetic acid? So far I have hesitated to do so, first for fear the patient would assume too much responsibility and second, because it would simply add to the worries of the diabetic life Without it the coma mortality for all my patients similarly scattered was but 6.1 per cent for 981 deaths between January 1, 1930 and March 13, 1935

The patients themselves are fairly innocent of the charge of dying of coma I am sure you would agree if you read the accounts which I receive It would hardly do to print them because the laity would not realize that although the coma mortality for childhood cases is shockingly high, the rate of decrease is rapid and during the next five years probably the decline will go on and be accelerated And my reasons for this belief are that at present patients are taught more about their disease, doctors who are more conversant with insulin are in the saddle, and laboratory facilities, although often still deficient and in many localities unavailable at night and upon holidays and Sundays, are multiplying

Mobile coma units should be organized for areas without first class laboratories These might consist of (1) a technician with an outfit for analysis of urine, blood sugar, CO_2 combining power, non-protein nitrogen and sodium chloride, (2) a nurse and (3) a doctor The expense for furnishing such an outfit is relatively trifling compared with the cost of a neglected coma case in a hospital and it could operate throughout a radius of 100 miles It is unlikely that it would need to go many times to the same section, because the benefit which would accrue from it would be so obvious that the community would recognize and provide for the same

Each diabetic child must always be recognized as a coma possibility and thus the patient, the relatives and the family doctor should realize On this account, I believe there should be in advance a plan for hospital accommodations not only for coma but for all diabetic emergencies However, discretion must be exercised in giving instruction to patients upon medical subjects and this holds particularly for diabetic coma It is all right to picture the ease with which diabetic patients go into coma, but for very obvious reasons the disagreeable symptoms attending the process, as well as the discomforts of treatment should be stressed else in a moment of discouragement patients might deliberately welcome it as a means to an end

Pulmonary Tuberculosis Tuberculosis does not develop unannounced and it seems a shame that diabetic children who are so intimately in contact with the medical profession should acquire it, much less die of it In the first quinquennium following Banting's discovery we had no deaths from

tuberculosis and this applies as well to the entire group of children I saw prior to 1922 even as far back as 1898. The reason is plain—children did not live long enough in that period to acquire tuberculosis, or, if they did develop it, death from coma carried them off before tuberculosis became the lethal factor. Later between 1927 and 1932, when the average duration of diabetes for the 27 fatal cases in children had reached 4.7 years, tuberculosis caused two deaths (7 per cent) and in the next five years, 1932–1937, when the duration was nine years, there were seven cases (17 per cent) among the 42 deaths, making a total of nine fatalities from tuberculosis in the last 15 years. I might add that of my five fatal cases in children whose diabetic duration was 15 years or more, there was one death or 20 per cent from tuberculosis and, in fact, of the 10 deaths with a diabetic duration between 10 and 15 years there were four or 40 per cent from tuberculosis. From the above, it is plainly evident how essential it is to look for tuberculosis in diabetic children because it is almost as preventable and as needless as diabetic coma.

The ages, dates of onset of tuberculosis and of diabetes, and dates of deaths are given in table 2. Four of the children were males and five females. We have warned girls especially about tuberculosis because these five included two who had taken up nursing and the tuberculosis followed. Now we say no diabetic girl should become a nurse.

TABLE II
Nine Instances of Tuberculosis in 104 Deaths of Diabetic Children

Case No	Sex	Birth Date	Onset				Death	
			Diabetes		Tuberculosis			
			Date	Age	Date	Age	Date	Age
2274	M	Jan 1915	Jan 15, 1921	6 0	Jan 1927	12 0	Feb 13, 1934	19 1
3795	F	May 2, 1910	Dec 15, 1923	13 0	Jan 1930	19 7	Mar 17, 1930	19 8
3957	M	Jan 22, 1912	May 10, 1924	12 3	Nov 1932	20 8	Aug 10, 1933	21 6
4232	F	Aug 21, 1907	Sept 1921	14 1	Mar 23, 1928	20 6	Nov 25, 1936	29 3
4743	F	June 9, 1908	March, 1923	14 8	Nov 1931	23 4	May 25, 1936	27 9
5932	M	June 4, 1913	Feb 1927	13 7	Jan 1932	18 6	March 18, 1937	23 8
7041	M	Jan 24, 1916	April, 1922	6 3	Feb 1930	14 1	Oct 30, 1930	14 8
7047	F	Jul 27, 1917	June 5, 1928	10 9	May, 1934	16 8	Jan 1935	17 5
12385	F	June 7, 1919	Jan 1929	9 6	Nov 1933	14 4	Jan 9, 1934	14 6

The duration of the diabetes before the onset of the tuberculosis in no instance was less than 4.9 years and it did not exceed 8.6 years. The total duration of the diabetes varied between 5 years and 15.2 years and averaged 9.8 years which is actually greater by 2.4 years than for the 15 cases with onset in childhood dying from all causes in the first decade of life between January 1, 1930, and March 13, 1935, and 3.3 years greater than for the

29 cases with onset in childhood dying in the second decade of life in the same period

The duration of the tuberculosis from its onset until death varied between 0.1 of a year and 7.1 years. In five of the nine cases, it was less than one year. It is only fair to add, however, that we now have four living children with tuberculosis, and two with tubercle bacilli in the sputum. The tuberculosis has gone on in these living cases from 2.6 to 9.3 years.

The high incidence of tuberculosis in diabetic children was first called to my attention by my colleague, Howard F. Root, in 1934. At that time, he found it was 13 times as great in our diabetic group as in the comparable group of school children in Massachusetts. Therefore, we know how near the danger is. Incidentally, he also showed the extraordinary frequency of tuberculosis following recovery from diabetic coma in our own coma series. He found that within three years following recovery from coma, one in eight of our patients developed tuberculosis of the lungs. Since it happens that 10 per cent of our diabetic children at one time or another go through an attack of diabetic coma we have here a predisposing factor. But tuberculosis does not originate *de novo* and Dr. Root tells me that among these nine deaths from it in our children's series there was obvious exposure in four instances.

How shall this second group of needless deaths of diabetic children be averted? 1. Remembering the high incidence of tuberculosis in diabetic children much more energy should be expended both to prevent it and to detect it early. It is not a question of skill, but plain hard work and the use of well known methods. Tuberculin tests should be done yearly and if positive followed up by roentgen-rays. Moreover these rules should apply increasingly as long as the patients live. It costs us doctors nothing to secure a Wassermann test for our diabetic children and we never fail to take such, although as yet we have never had one positive. To secure a roentgenogram of the chest of a child, however, entails an expense which may reach \$15. The means for securing roentgen-rays should be simplified.

Infections Infections apart from tuberculosis have claimed 17 diabetic children and in a rising percentage for the three five-year periods from 9 to 11 to 26 per cent. Elsewhere when the follow-up of all our children for 1937 is complete, we shall report these in detail.

Hypoglycemia Hypoglycemia was responsible for four deaths. These cases already have been reported elsewhere. The first was soon after the discovery of insulin, far from Boston, and in an excellent hospital. The poor little child was wasted with a long standing infection, had undergone a multitude of therapeutic procedures, blood sugar tests were then made only with venous blood and what proved to be the crucial test, I understand, was postponed with the best intentions by a tender-hearted house officer until too late. The second death was in a child who sang in the choir Sunday night, had a convulsion the following morning at 2 a.m. and the

diagnosis being mistaken for diabetic coma received 200 units of insulin from a doctor who had never seen a case of coma or of an insulin reaction and at the moment was caring for a pregnant woman. Details about the other two are unsatisfactory and hypoglycemia was not demonstrated.

Miscellaneous In this group are included two deaths by trauma and one reported as cerebral hemorrhage. There are also two deaths during pregnancy.

Pregnancy occurs rather frequently among our girls who have outgrown childhood and although it can be successfully undergone there are real risks unless the greatest precautions for care during its course and at delivery are taken. Among our group of girls with onset of diabetes in childhood and now above the age of 18 years we know of at least 28 instances of pregnancy. We do know that in 26 the result was without harm to the mother, but there were two deaths—7 per cent—or fully 14 times the standard rates! Elsewhere these cases will be reported in detail by my colleague, Dr. Priscilla White.

CONCLUSIONS

When one contemplates the mortality of these children and realizes that 82 of them, 79 per cent, died needlessly—69 of coma, 9 of tuberculosis, 4 of hypoglycemia—and possibly that some of the others might have been saved with more alert and expert treatment during their infections or pregnancy, it is evident that the present mortality of diabetic children is a remediable and therefore a hopeful index of the future of the diabetic child.

August 7, 1937, begins the fourth quinquennium since my use of insulin and at its end I am confident a brighter report can be made than hitherto. It demands no new discovery, but only that same persistent, individual and educational effort for each child which Dr. Joseph H. Pratt displayed in the organization of his first tuberculosis class. That class suggested to me the educational methods which I have employed in the treatment of my diabetics and it is a satisfaction to record here my whole-hearted and appreciative recognition of his help.

EDITORIAL

POSTGRADUATE COURSES FOR MEMBERS OF THE COLLEGE

A fundamental purpose of the American College of Physicians is to raise the level of the practice of internal medicine. Important steps have been taken towards the attainment of this objective.

The development of the membership of the College to include a majority of the more outstanding clinicians, teachers and investigators of this country has in itself been important since it increases the prestige attached to membership in the College. Membership in the College thereby becomes a natural goal of the ambitious young internist. Since membership is to be won by furnishing evidence of careful study of teaching or research, of publications as well as of high ethical standards in practice, the more the College attracts young men the greater will be the influence of the College upon the future standards of internal medicine.

In its participation in the establishment and in the direction of the American Board of Internal Medicine the College has again demonstrated its belief that the title of internist should connote definite and serious study, training and experience. The requirements made of the applicant are not rigid but to meet them will require a training which is broader and more intensive than that usually afforded by the medical internship and residency. In many instances such training has been too exclusively a bedside apprenticeship to a few senior clinicians plus a large quota of time devoted to the routine details of administration of a medical service. No provision has been made for orderly study of the pathologic physiology of disease, nor for advanced training in the methods of clinical pathological research. With the exception of a relatively few institutions most hospitals give to their Residents a type of training which was developed half a century ago when all the hospital had to offer was concentrated clinical experience. It is certain that the establishment of the various Boards for the specialties is actively stimulating a revision of the whole residency system. These new years must be so reorganized as to give to the Resident more time for study, more systematic instruction, and a broader clinical experience than the average general hospital can furnish on its wards. Groupings of hospitals to furnish complete training, and alliances of hospitals with nearby medical schools offer possibilities worthy of consideration. A period of rotation in special consultant clinics (cardiology, neurology, allergy, etc.) may also usefully supplement the ward and private patient experience of the Resident. It seems certain that in helping to establish the American Board of Internal Medicine the College has done a great deal to alter and improve the training of young internists.

These efforts of the College to raise the level of training for young physicians are, however, only a part of its educational program. From the

earliest days the best known activity of the College has been its Annual Session, and what is the significance of this week-long meeting if it is not a wholesome acknowledgment of the fact that the need for medical education does not stop when Fellowship in the College has been attained? Indeed the College is made up of a fellowship of students—life long students of the art of medicine,—and not by any means of a faculty of instructors. It is this eager interest on the part of the Fellows for the latest and the best in medical knowledge that adds so greatly to the stimulating atmosphere of our Annual Sessions. During that time we are all students together in a temporary school of our own creation.

This year will witness one of the most valuable of the Annual Sessions, since for the first time since very early days we are to meet in New York and to have laid before us the tremendous resources and activities of its great medical institutions. It seems certain that there will be a gathering of the membership of record breaking proportions.

This year witnesses also an innovation—the establishment by the College of a group of Postgraduate Courses for Fellows and Associates during the two weeks preceding the Annual Sessions which begin on the fourth of April. Each Fellow and Associate has already received the preliminary announcement from the Committee on Postgraduate Courses appointed by the Regents. The courses are offered at Harvard and Columbia Universities and at the University of Pennsylvania. In addition to general medicine there are to be special courses in the neuropsychiatric aspects of medicine, in metabolism, cardiovascular diseases and gastrointestinal diseases.

It is only through trial efforts of this type that the needs and the desires of the members of the College can be discovered. The establishment of such timely opportunities, which extend the postgraduate study period of the Annual Sessions, is to be looked on as a logical development of the essential program of the American College of Physicians.

REVIEWS

The Diagnosis and Treatment of Pulmonary Tuberculosis By JOHN B HAWES, M D, and MOSES J STONE, M D 215 pages, 14 X 21 cm Lea and Febiger, Philadelphia, Pa 1936 Price, \$2.75

This brief and concise textbook on pulmonary tuberculosis, in our opinion, fulfills a very definite and until now unsatisfied need in this field. It confines itself to the essentials of the disease and does not include theoretical discussions of the intricate and highly specialized subjects of immunity, resistance, allergy, etc. The student is referred in an excellent bibliography at the end of each chapter to more complete and larger works.

There are sections on the history of the disease, on history taking, on physical examination, on constitutional and local symptoms, on childhood tuberculosis, on the treatment of the disease and on tuberculosis in pregnancy and in industry.

The authors show great ability to compress the discussion of facts into small space without losing clearness or interest. Mature experience has enabled them throughout to justly distribute the emphasis so as to enable the reader to discern between the essential and the less important facts.

This excellent book should be in the hands of every practitioner of medicine and should be a standard of instruction for medical students. The manner of presentation, the data given and the bibliography make it worthy of the attention of all interested in tuberculosis.

Synopsis of Clinical Laboratory Methods By W E BRAY, B A, M D 324 pages, 12 X 19.5 cm C V Mosby, St Louis 1936 Price, \$3.75

An amazing amount of valuable information is contained in this small volume. Included are: A chapter listing the usual tests required by the various general and special hospital services, chapters on urinalysis (including diagnosis of pregnancy), on hematology, blood chemistry, gastric analysis, feces and intestinal parasites, puncture fluid examination and cerebrospinal fluid, sputum, bacteriology, water and milk examination, serology, basal metabolism, allergy tests, poisons and foreign substances, surgical pathology, and a chapter of formulae and a table of normal values.

Precautions to be observed in the collection of specimens and performance of tests are emphasized. A succinct statement of interpretation follows each method given.

In a book which is so modern in all other respects it is unfortunate that the author adheres to the older bacteriological nomenclature. There are very few errors of statement or typography. The choice of technics included seems judicious.

The summary treatment of topics makes the book more valuable as a guide to the trained technician or as a supplement to more detailed works on the subject than for use by the inexperienced as a single source. It is highly recommended as a reference.

J H M

Developmental Abnormalities of the Eye By IDA MANN, D Sc, M B, B S (London), F R C S (Eng) 444 pages, 16 X 24 cm Published for the British Journal of Ophthalmology by the Cambridge University Press 1937 Price, \$15.00

This book is divided into eleven chapters. The first three deal with general considerations as to how abnormalities of the eye develop as well as general abnor-

malities of both the skull and the eye. Chapters IV and V are in reference to abnormalities of the fundi, VI of the iris, VII of the iris and vitreous, VIII of the lens, IX of the cornea, X of the conjunctiva and sclera, and XI of the lids, lachrymal apparatus and the orbit.

In her consideration of the subject Miss Mann has not only described congenital abnormalities but also those abnormalities that develop later. Her previous study of the embryology of the eye combined with the clinical material as seen in her own and her colleagues' clinics makes the work doubly authoritative. There may be some disagreement with the author concerning the theories advanced as to the mechanism of some of the developmental defects but those proposed seem quite logical.

The first three chapters which deal with the production of developmental abnormalities as well as abnormalities of the head and the orbit, will be of interest to anatomists, neurologists and internists. The remaining chapters are of more especial interest to the ophthalmologists and will help to elucidate many an obscure finding.

The book is most excellent in its illustrations of which about 50 are completely or partially in color. The printing is clear and while a few errors of spelling and reference are noted, the book is to be highly recommended.

C A C

The Roentgenologist in Court By SAMUEL WRIGHT DONALDSON, A B, M D, F A C R. 230 pages, 15 X 24 cm. Charles C Thomas, Springfield 1937. Price, \$4.00.

This book is the result of much reading of the law in its relation to the practice of medicine, supported by extensive personal experience on the witness stand. It is a well written, concise and authentic work on a subject too often neglected by the busy physician. As its title implies, the book is supposed to concern itself primarily with the law in its relation to the roentgenologist, but the legal aspect of the practice of roentgenology differs very little from the practice of medicine in general, and consequently it contains very little that has not been said before. The chapters on "X-Ray Films and Evidence," "Ownership of Films" and "Conclusions" are of special interest to radiologists, but can be read with profit by every physician who is apt to be called upon to testify in cases where roentgen examinations have been made. Too much space has probably been given to the citation of selected cases and court decisions, that have but little bearing upon the medical witness. The increasing frequency of law suits and the blind faith that so many people place in the use of the x-rays, regardless of the qualifications and experience of the physician who made the examinations, bring the roentgenologist into court more frequently than many of his confreres. Any physician who is apt to be called as a witness will be sure to find his court experience less onerous after a careful perusal of this small volume. It is sure to find a welcome reception in the library of radiologists. It also contains much of value to members of the legal profession who are confronted in the court room with the presentation and interpretation of roentgen-ray films.

H J W

Vascular Disorders of the Limbs By SIR THOMAS LEWIS, C B E, F R S, M D, D Sc, LL D, F R C P, Physician in Charge of Department of Clinical Research, University College Hospital, London. 111 pages, 16 X 22.5 cm. The Macmillan Company, New York. 1936. Price, \$2.00.

This small volume can be highly recommended to practitioners and students. In it are found simple methods of testing circulation to the limbs and descriptions of disorders affecting the circulation of the limbs such as embolism and thrombosis post-ischemic contractures, arteriosclerosis, thromboangitis obliterans, Ray-

naud's disease, acrocyanosis, erythrocyanosis and erythralgia. There are chapters dealing with the effects of circulatory arrest, arterial spasm, vasodilation and vascular disorders in diseases of the nervous system. The mechanisms and the treatment of these disturbances are described. Explanations of the maladies discussed are largely drawn from the author's researches published elsewhere. It should be noted that the author continues to attribute pain in circulatory arrest to the accumulation of products of muscular metabolism whereas evidence has been offered that this is not the sole factor. The book is remarkably condensed and at times this is annoying. One does not like to be referred to past or future discussions too frequently.

W S L, JR

Maternity and Post-Operative Exercises By MARGARET MORRIS, C S M M G 152 pages, 22 × 13.5 cm, Oxford University Press 1936 Price, \$2.00

The author is the founder of the International Institute of Margaret Morris Movement, and states that she has intended the book primarily for masseuses, midwives, and nurses who have taken the diploma of the Institute. However, surgeons, internists, and especially obstetricians may read this book with profit.

There are seven chapters of which five comprise the text material, and the last two describe the exercises in diagrams and words, and give exercise charts for specific indications. There is no index. The book is well printed in pleasing form.

The indications, precautions, effects, and anatomic and physiological reasons for the various exercises are carefully described. Individual exercises are described in words accompanied by clear and easily understandable original outline drawings by the author. The basic importance of proper breathing during the performance of the exercises is stressed. All the exercises are gently progressive. A special group of corrective exercises is outlined.

It is hoped that the members of the medical profession will be interested in this book, since the author stresses that the exercises should be carried out under medical supervision.

J E S

COLLEGE NEWS NOTES

GIFTS TO THE COLLEGE LIBRARY

Grateful acknowledgment is made of the receipt of the following donations to the College Library of publications by members

Books

- Dr Jacob C Geiger (Fellow) and Paul J Hanzlik (Fellow), San Francisco, Calif —“ A Handbook of Accepted Remedies Symptoms and Treatment of Poisoning, Diagnostic Procedures, Miscellaneous Information ”,
Dr Raphael Isaacs (Fellow), Ann Arbor, Mich, and Dr Hiram B Weiss (Fellow), Cincinnati, Ohio—“Manual of Clinical and Laboratory Technic ”,
Dr Frederick R Taylor (Fellow), High Point, N C—reprints of Chapters XII-A on “ Albinism,” XL-A on “ Arachnidism The Clinical Effects of Spider Bite ” and XLIII-A on “ Unusual Diseases and Symptom-Complexes not Discussed in Other Chapters (continued) ” from the Oxford Loose Leaf Medicine

Reprints

- Dr Norbert Enzer (Fellow), Milwaukee, Wis —1 reprint
Dr William W Graves (Fellow), St Louis, Mo —12 reprints
Dr Paul J Hanzlik (Fellow), San Francisco, Calif —4 reprints
Dr Elwood A Sharp (Fellow), Detroit, Mich —5 reprints
Dr Barnett Greenhouse (Associate), New Haven, Conn —1 reprint
Dr Florimond LeBlanc (Associate), Elgin, Ill —1 reprint
Dr Robert P Wallace (Associate), New York, N Y —1 reprint
Dr John O Woods (Associate), New Castle, Pa —1 reprint

Dr E J G Beardsley (Fellow and Governor for Eastern Pennsylvania for the College) Philadelphia, was the guest of the Westmoreland County Medical Society at Greensburg (Pa), on November 9 A clinic of patients exhibiting various cardiovascular disorders was held in the Westmoreland Hospital

Dr Beardsley also addressed the members of the Atlantic County (N J) Medical Society, Atlantic City, November 12, on “ The Man of Fifty ”

Dr William R Brooksher (Fellow), Fort Smith, has been appointed a member of the advisory council of the maternal and child health division of the Arkansas State Board of Health

The twelfth annual series of Friday Afternoon Lectures of the New York Academy of Medicine began November 19 The following Fellows of the College were scheduled to give lectures

November 19, Dr Robert L Levy, New York, “ Drugs in the Treatment of Heart Disease ”,

December 17, Dr Eugene M Landis, Philadelphia, “ Recent Advances in the Diagnosis and Treatment of Peripheral Vascular Diseases ”

Dr Lewis B McBrayer (Fellow), Southern Pines, N C, has retired as managing director of the North Carolina Tuberculosis Association, which position he has held since 1915, when the association was founded. Dr McBrayer also resigned as secretary of the Medical Society of the State of North Carolina

Dr David I Abramson (Associate), Brooklyn, has been appointed director of the department of cardiovascular research at the Jewish Hospital, Cincinnati

Dr Alex F Robertson, Jr (Fellow), Staunton, was elected president-elect of the Medical Society of Virginia at the annual meeting at Roanoke, October 12-14

Dr A Comingo Griffith (Fellow and Governor for Missouri), Kansas City, was recently elected president of the Jefferson D Griffith Chapter of the Association of Military Surgeons

Dr Elmer L Sevringhaus (Fellow), Madison, Wis, and Dr Arlie R Barnes (Fellow), Rochester, Minn, were guest speakers at the annual meeting and clinical conference of the Southwestern Medical Association, held at Phoenix, Ariz, November 18-20

Dr J Arthur Myers (Fellow), Minneapolis, addressed the annual public meeting and "health crusade" of the District of Columbia Tuberculosis Association, November 22, on "Modern Methods in the Control of Tuberculosis"

Dr Elliott P Joslin (Fellow), Boston, was a guest speaker on the dedicatory program of the new building of the Evangelical Deaconess Hospital, Detroit, November 10

Dr Arthur M Master (Fellow), New York, delivered the third of a series of lectures on heart disease, sponsored by the New York Heart Association, December 14, on "Use of Electrocardiograms in the Diagnosis and Prognosis of Coronary Thrombosis"

Dr S Spafford Ackerly (Fellow), Louisville, was elected vice president of the recently organized Kentucky Psychiatric Association at a meeting in Lexington

The Northeastern Indiana Academy of Medicine was addressed at Kendallville, October 28, by Dr Arthur E Mahle (Fellow), Chicago, on "Recent Advances in Medical Management of Peptic Ulcer"

At a meeting of the Hennepin County Medical Society, Minneapolis, November 10, Dr Carl V Weller (Fellow), Ann Arbor, spoke on "Intrinsic Factors in the Causation of Cancer"

Dr J Arthur Myers (Fellow), Minneapolis, president of the National Tuberculosis Association, was the guest speaker at the annual meeting of the New Jersey Tuberculosis League in New Brunswick, October 22

At the annual dinner of the Association for the Advancement of Industrial Medicine and Surgery, held October 20, Dr Albert E Russell (Fellow), U S Public Health Service, spoke on "Syphilis Control in Industry"

Dr B B Vincent Lyon (Fellow), Philadelphia, was a guest speaker at the sixth annual graduate program of the Summit County (Ohio) Medical Society Dr Lyon spoke on "Methods of Diagnosis and Treatment of Cholecystitis" and "Diagnosis and Management of Peptic Ulcer"

Dr Samuel B Scholz, Jr (Fellow), Philadelphia, was elected president of the Association of Life Insurance Medical Directors at the annual meeting in New York City recently

At its meeting in San Francisco in October, the Association of American Medical Colleges elected Dr Willard C Rappleye (Fellow), Dean of the College of Physicians and Surgeons of Columbia University, New York, as its president-elect, while Dr William S Middleton (Fellow), Madison, Wis, was elected vice president

The thirty-third annual meeting of the American Society of Tropical Medicine was held in New Orleans, November 30-December 3, in conjunction with the Southern Medical Association Dr George W McCoy (Fellow) of the U S Public Health Service delivered the second Charles Franklin Craig Lecture on "The History of Leprosy in the United States" Another guest speaker at the sessions was Dr William M James (Fellow and Governor for Panama and the Canal Zone for the College), Panama, R P, who spoke on "Emetine Therapy"

Dr Priscilla White (Fellow), Boston, was a guest speaker at the Fifth Annual Scientific Meeting of the Georgia Pediatric Society, December 9 Dr White spoke on "Endocrine Problems in Juvenile Diabetes" and "Recent Problems in Juvenile Diabetes"

Memorial rooms for the late Dr Henry R M Landis (Fellow), Philadelphia, for many years director of the clinical and sociological departments of the Henry Phipps Institute, University of Pennsylvania, have been established in the suite he occupied at the Institute

The following Fellows of the College were guest speakers on the program of the Southern Medical Association's annual meeting at New Orleans, November 30-December 3

Dr Stewart R Roberts, Atlanta, Ga , "Your Health and Mine",
Dr Robert A Cooke, New York, "Medical Problems of the Allergist",
Dr Priscilla White, Boston, "Protamine Insulin in the Treatment of Juvenile Diabetes",
Dr Walter C Alvarez, Rochester, Minn , "Some Stages in the Development of Gastro-Enterology",
Dr Lawrence Reynolds, Detroit, "Pulmonary Cysts",
Dr William D Cutter, Chicago, "The Appraisal of Medical Schools"

Dr Henry I Klopp (Fellow), Allentown, Pa , has been superintendent of the Allentown State Hospital since its founding. On October 12 the twenty-fifth anniversary of the opening of the hospital was celebrated with a special program. Dr James Allen Jackson (Fellow), Danville, Pa , presented a paper on "Extra-Institutional Clinical Activities in Twenty-Five Years". An oil painting of Dr Klopp was unveiled as the gift of the medical societies of Lehigh, Northampton and Bucks counties and the Lehigh Valley Homeopathic Society.

Dr William Gerry Morgan (Fellow), Washington, D C , was the chief guest speaker at the annual staff banquet of the Reading (Pa) Hospital on November 3, 1937. Dr Morgan was a resident intern at the old Reading Hospital in 1893. Memorials to two physicians, Dr Charles H Hunter, one of the founders of the hospital, and Dr Charles G Loose, for fifty-three years a member of the staff, and to Mr Gustav R Oberlaender, for many years President of the Board of Directors, were unveiled.

Solomon Strouse (Fellow) has recently received the following appointments: Associate Clinical Professor of Medicine at the University of Southern California, Attending Physician at the Los Angeles County General Hospital, Visiting Physician at the Cedars of Lebanon Hospital, Los Angeles, California.

Dr William C Voorsanger (Fellow), San Francisco, has been elected president of the San Francisco County Medical Society for the year 1938.

Dr David Riesman, Professor of the History of Medicine in the University of Pennsylvania, and Professor of Clinical Medicine in the Graduate School of the University, delivered the Vanuxem lectures at Princeton University on December 7, 8, 9 and 10. The lectures were on the general topic "Medicine in Contemporary Culture," the first being on "Medicine—Art and Science", the second, on "Superstitions, Cults and Medical Ethics", the third, on "The Family Doctor, Past and Future" and "Medicine as a Career", the fourth, on "The Social Outlook in Medicine".

Dr Carl J Wiggers (Fellow), Professor of Physiology, Western Reserve University, School of Medicine, has recently returned from the Orient, where he delivered a series of 16 lectures in Canton, Hong Kong, Shanghai, Peiping, Seoul, Kyoto and Tokyo. Professor Wiggers has accepted an invitation to address the Sixth National Congress of Medicine in Cordoba, Argentine, in October 1938, the other

guest speakers being Professor Gregorio Marañón from Madrid and Professor Volhard from Germany

The Annual Meeting of the Illinois Members of the American College of Physicians outside of Chicago was held at Bloomington, Illinois, on October 14, 1937, under the chairmanship of Dr Samuel E Munson, Governor Dr Edgar M Stephenson and Dr Gerald M Cline served as a Committee on Arrangements The meeting began at 3 o'clock in the afternoon and an interesting medical program was presented

- "Arterio-Sclerotic Heart Disease," Dr Nathan S Davis, III, Chicago, Ill, Assistant Professor of Medicine, Northwestern University Medical School
- "Current Endocrine Problems in Gynecology," Dr Elmer R Sevringhaus, Madison, Wisconsin, Associate Professor of Medicine, University of Wisconsin Medical School
- "Peripheral Circulatory Failure," Dr Louis M Warfield, Milwaukee, Wisconsin, Former Professor of Clinical Medicine, Marquette University, Former Professor and Head of the Department of Medicine, University of Michigan
- "The American Board of Internal Medicine, and Other Important Medical Questions," Dr Walter L Bierring, Des Moines, Iowa, Chairman, American Board of Internal Medicine, Past-President, American Medical Association

Dr Munson, as Chairman, reviewed for the Fellows of the College present the events of the last year in the history of the College and rendered a tribute to Dr Frank Smithies whose death has occurred since the preceding Annual Regional Meeting, at which he had been present as a guest and speaker

The afternoon program was followed by dinner at 6 30 and adjournment at 10 00 o'clock The meeting was excellently attended by Fellows of the College from Illinois

ABSTRACT OF MINUTES OF THE BOARD OF REGENTS

PHILADELPHIA, PA

December 12, 1937

A regular meeting of the Board of Regents of the American College of Physicians was held December 12, 1937, at the College Headquarters, Philadelphia, Pa, the meeting being called to order at 10 20 a m by President James H Means, with the following present

James H Means, President
William J Kerr, President-Elect
David P Barr, First Vice President
William D Stroud, Treasurer
George Morris Piersol, Secretary-General
James B Herrick
Robert A Cooke
Jonathan C Meakins
Hugh J Morgan
James E Paulin
James D Bruce
Egerton L Crispin
James Alex Miller
Francis M Pottenger
Walter L Bierring
Ernest B Bradley
Roger I Lee
Sydney R Miller
Walter W Palmer
O H Perry Pepper
Maurice C Pincoffs
Charles H Cocke

and with the Executive Secretary, Mr E R Loveland, acting as secretary of the meeting

On motion by Dr Paulin, seconded by Dr Bierring and unanimously carried, the reading of the Minutes of the St Louis Meeting was dispensed with

Mr E R Loveland, Executive Secretary, read communications from Dr G Gill Richards and Dr William Gerry Morgan, the only absentees at the meeting

The secretary also read several communications from public officials, physicians and one in particular from Dr Willard C Stoner, renewing the invitation from the City of Cleveland for the College to convene there in 1939

The Executive Secretary further read a set of communications from public officials, the Academy of Medicine and, in particular, from Dr Julien E Benjamin, presenting an official invitation for the College to convene in Cincinnati in 1939 Mr Loveland reminded the Board that invitations are still outstanding from New Orleans, San Francisco, St Paul and Washington for 1939

Dr Ernest B Bradley spoke in favor of the Cincinnati invitation, and expressed the opinion that Cincinnati's facilities and accommodations would be adequate for the College

On motion by Dr James E Paulin, seconded by Dr Sydney R Miller and regularly carried, it was

Resolved, that the Executive Secretary be instructed to visit, in advance of the New York Session in April, any of the cities from which invitations have been received, in order to inspect their facilities and accommodations

The Secretary brought to the attention of the Board that Dr Clement R Jones, of Pittsburgh, had presented a copy of the first edition and Dr C W Waddell, of Fairmont, W Va, had presented copies of both the first and second editions of the ANNALS OF MEDICINE, Volume I, 1920, to be added to the College archives. These were the first issues of the first journal sponsored by the American College of Physicians and the American Congress on Internal Medicine, but during the intervening years of changes in administration, all official copies of these issues had disappeared. The copies presented were in good state of preservation, and are a valuable addition to the College records.

On motion by Dr Roger I Lee, seconded by Dr James E Paullin, and regularly carried, it was

Resolved, that a vote of thanks be extended to the donors, Dr Clement R Jones and Dr C W Waddell.

Dr David P Barr, Chairman of the Committee on Fellowships and Awards, read communications by Dr George W Pickering, of London, and Dr Myron Prinzmetal, the 1936-37 Research Fellow, describing the work of Dr Prinzmetal during the year—Dr Pickering commending the College for awarding the Fellowship to Dr Prinzmetal, and Dr Prinzmetal expressing his deep appreciation to the College.

The following resolutions were unanimously adopted concerning the transfer of securities by the Treasurer some months previous.

Resolved, that the Treasurer of the American College of Physicians be and is authorized and directed, in accordance with the recommendations of the Finance Committee, to sell, assign and transfer fifty (50) shares General Motors common stock, Certificate No C643-886, in the name of this corporation.

Resolved, that the Treasurer of the American College of Physicians be and is authorized and directed, in accordance with the recommendations of the Finance Committee, to sell, assign and transfer forty-five (45) shares Mid-Continent Petroleum Company stock, Certificate No 7815, in the name of this corporation.

Pending the arrival of Dr George Morris Piersol, Secretary-General, President Means reported the following deaths of members since the preceding meeting of the Board of Regents as follows:

Fellows

Avery, Jacob Fowler	La Jolla, Calif	June 25, 1937
Behlow, William Wallace	Palo Alto, Calif	April 29, 1937
Betts, Arthur	Spokane, Wash	October 17, 1937
Breed, Lorena M	Pasadena, Calif	October 20, 1937
Brown, Douglas	Castle Point, N Y	June 6, 1937
Chester, John Leonard	Detroit, Mich	May 31, 1937
Crane, Augustus Warren	Kalamazoo, Mich	February 20, 1937
Daland, Judson	Philadelphia, Pa	August 14, 1937
Daley, Daniel Francis	Kingston, Pa	April 24, 1937
Dalton, Eugene S	Brooklyn, N Y	April 19, 1937
Dickie, Jamie W	Southern Pines, N C	July 6, 1937
Eggleston, Elmer L	Battle Creek, Mich	July 7, 1937
Elrod, John Oscar	Forsyth, Ga	April 21, 1937
Ferris, Albert Warren	East Orange, N J	October 4, 1937
Grewe, John Ernest	Cincinnati, Ohio	October 29, 1937
Hardin, Ronda Horton	Banner Elk, N C	October 9, 1937
Howard, Leroy Taylor	M C, U S Army	September 30, 1937

Landis, Henry R M	Philadelphia, Pa	September 14, 1937
Lemann, Isaac Ivan	New Orleans, La	September 2, 1937
Lyter, J Curtis	St Louis, Mo	October 9, 1937
Mason, Elijah Lumbia	Washington, D C	August 30, 1937
McCampbell, Eugene F	Columbus, Ohio	May 8, 1937
Miller, Joseph Leggett	Chicago, Ill	August 6, 1937
Myers, Harold Bunce	Portland, Ore	March 6, 1937
Oleson, Richard B	Lombard, Ill	August 6, 1937
Pothuisje, Peter Jurgens	Denver, Colo	June 4, 1937
Samenfeld, Joseph	Brooklyn, N Y	September 5, 1937
Sherrill, Coite Long	Statesville, N C	June 24, 1937
Smith, Munford	Los Angeles, Calif	June 28, 1937
Surnamer, Isaac	Paterson, N J	April 23, 1937
Sweet, Earl	Los Angeles, Calif	May 22, 1937
Walcott, Harry Gilmer	Dallas, Tex	June 2, 1937
Waples, Frank Alsworth	Houston, Tex	March 4, 1937
Warr, Otis Sumter	Memphis, Tenn	March 22, 1937
Wyckoff, John	New York, N Y	June 1, 1937

Associates

Calhoun, Abner Wellborn	Atlanta, Ga	November 3, 1937
Sprenkel, Vaughan LeRoy	Allentown, Pa	June 18, 1937
Walker, Thomas Tipton	Watertown, N Y	November 13, 1937

President Means also, on behalf of the Secretary-General, reported the following additions to the Life Membership Roster since the last Regents' meeting

Estella G Norman, Miami Springs, Fla
 Charles W Waddell, Fairmont, W Va
 Hugh Francis Crawford, Memphis, Tenn
 Louise Taylor-Jones, McLean, Va

These additions make a total of 83 Life Members, 4 of whom are now deceased, leaving a remainder of 79

Dr James E Paullin, Chairman of the Committee on Public Relations, reported as follows

(1) Resignations of the following be accepted

Colonel William Denton (Fellow), M C, U S Army
 Dr D Grant Campbell (Associate), Montreal, Que, Canada
 Dr George H Jantzen (Associate), Queens Village, N Y
 Dr Frederick H Lamb (Associate), Davenport, Iowa
 Dr Maurice T Root (Associate), West Hartford, Conn
 Dr Francis C Weber (Associate), Newark, N J
 Dr James H Wheeler (Associate), Henderson, N C

(2) That the request of Dr George H Spivey (Fellow), Hot Springs, S D, to be dropped from the Roster be acceded to

On motion by Dr James E Paullin, seconded by Dr Jonathan C Meakins, and unanimously carried, it was

Resolved, that the Board of Regents approve in full the recommendations of the Committee on Public Relations embodied in the three sections above

Dr Paullin, for the Committee on Public Relations, then reported that a "communication from Dr Russell M Wilder, of the Mayo Clinic, including a letter to Dr James H Means, President of the American College of Physicians, concerning

newspaper publicity in the *Chicago Daily Times*, has been received and read Your Committee is in sympathy with the predicament in which the Mayo Clinic finds itself and with the embarrassing position in which they are placed, but it knows of no remedy which can be utilized to overcome such publicity"

On motion by Dr Paullin, seconded by Dr Jonathan C Meakins and unanimously carried, it was

Resolved, that the Board of Regents approve of this part of the report of the Committee on Public Relations

Dr Paullin proceeded with his report "A communication from Dr Noiman Strauss, of New York City, in which he propounds two questions and asks for an expression of opinion by the Board of Regents concerning a division of fees, has been received It is the advice of the American College of Physicians that in professional dealings with patients, these be conducted openly and frankly, and that the principles of the medical ethics of the American Medical Association be followed, and that there shall be no fee-splitting and no attempt whatsoever made either at evasion or circumvention of these principles Bills for medical services presented by various practitioners should be rendered separately, in order that no suspicion of motive be aroused A copy of this reply to Dr Strauss should be sent to Dr Olin West, Secretary of the American Medical Association, Chicago, and to Dr George E Follansbee, Chairman of the Judicial Council of the American Medical Association, 629 Euclid Ave, Cleveland, Ohio, together with a copy of the Pledge, which each member of the American College of Physicians takes on induction into Fellowship"

On the suggestion of Dr James Alex Miller, the recommendation of the Committee was amended, providing for the insertion of the following "Consequently, both questions submitted by Dr Strauss are in violation of these principles"

On motion by Dr Paullin, seconded by Dr James Alex Miller and unanimously carried, it was

Resolved, that the Board of Regents approve of the above section of the report of the Committee on Public Relations

Dr Paullin continued the report of his Committee "A communication from Dr Paul D Abramson, Secretary of the Shreveport Medical Society (Shreveport, La), was received and read It is the opinion of your Committee that the American College of Physicians has no suggestion to make concerning this resolution (regarding an Act of their State Legislature constituting a State Hospital Board and opening charity state hospitals), and we respectfully refer the Shreveport Medical Society to the American Medical Association, who would properly have jurisdiction over such matters"

On motion by Dr Paullin, seconded by Dr F M Pottenger, and unanimously carried, it was

Resolved, that the Board of Regents approve of the above section of the report of the Committee on Public Relations

Dr Paullin proceeded with his report "Your Committee is in receipt of a set of resolutions from the Committee of Physicians, of which Dr John P Peters, of New Haven, Conn, is the secretary, in which certain principles and proposals are outlined, and which have been signed by 430 physicians of the United States We are also in receipt of another set of principles submitted by Dr Eugene S Kilgore, of San Francisco In addition, there is a letter from Dr Henry M Thomas, Jr, Governor of the College for Maryland Your Committee feels that these resolutions and proposals should be brought to the attention of the Board of Regents as a whole, without any recommendation of the Committee on Public Relations"

On motion by Dr Paullin, seconded by Dr Charles H Cocke, and unanimously carried, it was

Resolved, that these proposals and recommendations be received and filed with the secretary

Dr David P Barr, Chairman of the Committee on the ANNALS OF INTERNAL MEDICINE, reported that the Committee is profoundly satisfied with the progress of the ANNALS, and while it is quite possible that various extensions of activity could be made, the work that the ANNALS is now doing seems to the Committee very good indeed, and, therefore, no specific recommendations were brought before the Board. However, he expressed the opinion that sooner or later the Editor would need additional help, particularly if new departments in the ANNALS are to be established. One of the matters discussed by the Committee was that of a department for postgraduate education, a service to internists and physicians throughout the country, which would keep them informed of postgraduate courses available here and abroad. There had also been some discussion of extension of monographs or special articles, similar to the one on rheumatism, which appeared several years in the ANNALS. The Committee in conclusion reported that in spite of a materially increased size of the ANNALS during the past year and, consequently, increased expenses, the ANNALS still is splendidly solvent.

On motion by Dr George Morris Piersol, seconded by Dr William D Stroud, and unanimously carried, it was

Resolved, that the report of the Committee on the ANNALS OF INTERNAL MEDICINE be adopted

Dr Sydney R Miller, Chairman of the Committee on Credentials, presented his report "The Committee has considered 95 candidates for Fellowship and 183 candidates for Associateship. An analysis of the recommendations of the Committee concerning candidates for Fellowship is as follows

47 to be advanced from Associateship
19 direct elections
14 to be advanced from Associateship 'as of April 3, 1938'
2 recommended for Associateship
8 deferred
5 rejected
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95

"An analysis of the action recommended by the Committee in connection with the candidates for Associateship is as follows

146 elected Associates
2 elected Fellows
7 deferred for additional credentials
28 rejected
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183

Typed lists of all candidates were distributed for use by each member of the Board of Regents"

On motion by Dr Sydney R Miller, seconded by Dr James E Paullin, and unanimously carried, it was

Resolved, that the following list of 68 be and herewith are elected to Fellowship in the American College of Physicians as of this date, December 12, 1937

*Candidates**Sponsors*

ALABAMA

Kyle Johnston Kinkead, Birmingham

James S McLester, Seale Harris, Fred Wilkerson

CALIFORNIA

Joseph A Polha, Los Angeles

John V Barrow, Samuel M Alter, James F Churchill

Neville Thompson Ussher, Santa Barbara

Hilmar O Koefod, F M Pottenger, James F Churchill

COLORADO

Thomas D Cunningham, Denver

J N Hall, James R Arneill, Gerald B Webb

Edgar Durbin, Denver

James J Waring, R W Arndt, Gerald B Webb

Lumir R Safarik, Denver

Lorenz W Frank, John G Ryan, Gerald B Webb

Edwin Trueman Thorsness, Denver

Wilfred S Dennis, W Bernard Yegge, Gerald B Webb

MEDICAL CORPS, U S ARMY

Sanford Williams French, Fort Washington, Md

C R Reynolds

MEDICAL CORPS, U S NAVY

John Harper, Washington, D C

W A Bloedorn, P F Dickens, Dallas G Sutton

Frederick Leonard McDaniel, Washington, D C

Charles S Butler, Walter Freeman, Dallas G Sutton

DISTRICT OF COLUMBIA

Isaac Judah Silverman, Washington

Eugene R Whitmore, C B Conklin, Wallace M Yater

GEORGIA

Joseph Howard Hines, Atlanta

Russell H Oppenheimer, H Cliff Sauls, Glenville Giddings

Champneys Holt Holmes, Atlanta

Allen H Bunce, Trimble Johnson, Glenville Giddings

ILLINOIS

Lee Connel Gatewood, Chicago

Lowell D Snorf, Arthur E Mahle, James G Carr

KANSAS

Fred John McEwen, Wichita

Henry N Tihen, Harold W Palmer, Thomas T Holt

LOUISIANA

Willard Ralph Wirth, New Orleans

Randolph Lyons, John A Lanford, J E Knighton

MARYLAND

Thomas Nelson Carew, Baltimore

M C Pincoffs, Louis Krause, Henry M Thomas, Jr

Richard France, Baltimore

Charles A Waters, Sydney R Miller, Henry M Thomas, Jr

Samuel Morrison, Baltimore

Julius Friedenwald, Theodore H Morrison, Henry M Thomas, Jr

*Candidates**Sponsors*~~MASSACHUSETTS~~

John Arthur Foley, Boston
Julian Carrel Gant, Boston

Francis Minot Rackemann, Boston

Olin Sewall Pettingill, Middleton

William Freeman, Worcester

Soma Weiss, W B Castle, William B Breed
Dwight L Siscoe, F Dennette Adams, William B Breed
J O Manier, George Morris Piersol, William B Breed
Francis Joseph Welch, Edward Alfred Greco, William B Breed
Erwin C Miller, George M Albee, William B Breed

MINNESOTA

Clement I Krantz, Duluth
Frank Hammond Krusen, Rochester
Louis Elwood Prickman, Rochester

Frank W Spicer, P G Boman, E L Tuohy
A R Barnes, E V Allen, E L Tuohy
E V Allen, Nelson W Barker, E L Tuohy

MISSISSIPPI

William Kendrick Purks, Vicksburg

W N Jenkins, L J Clark, G W F Rembert

MISSOURI

Edward Hagerman Hashinger, Kansas City
Delon A Williams, Kansas City

Logan Clendenning, Peter T Bohan, A C Griffith
Harry L Jones, Lindsay S Milne, A C Griffith

NEW YORK

Harold E Himwich, Albany
Henry M Feinblatt, Brooklyn
Arthur Edward Lamb, Brooklyn
William Henry Lohman, Brooklyn
James Moore Adams, New York
Waldo Beattie Farnum, New York
Franklin M Hanger, Jr, New York
Harry Julius Johnson, New York
John H Keating, New York
George Morris Lewis, New York
W Laurence Whittemore, New York
Abner Wolf, New York
Morris Eli Missal, Rochester

Harold Rypins, William Gerry Morgan, Walter W Palmer
Tasker Howard, George H Roberts, Jr, C F Tenney
Joshua M Van Cott, Nathan T Beers, C F Tenney
Tasker Howard, George H Roberts, Jr, Robert A Cooke, C F Tenney
Willard J Denno, O W Bethea, C F Tenney
James R Scott, Walter A Bastedo, Walter W Palmer
W W Herrick, W P Anderton, C F Tenney
Milton A Bridges, Arthur C DeGraff, C F Tenney
James R Scott, W P Anderton, Walter W Palmer
J Homer Cudmore, David Stanley Likely, C F Tenney
Willard J Denno, Russell L Cecil, C F Tenney
Charles A McKendree, Willard C Rappleye, C F Tenney
Charles B F Gibbs, William S McCann, Allen A Jones

NORTH CAROLINA

Thomas Preston White, Charlotte
Herman Richard Parker, Greensboro

Archie A Barron, E J Wannamaker, C H Cocke
Frederick R Taylor, D Waldo Holt, C H Cocke

OHIO

David Irvin Abramson, Cincinnati
(formerly of Brooklyn, N Y)

J Hamilton Crawford, George H Roberts, Jr, C F Tenney

*Candidates**Sponsors*

Harold Feil, Cleveland

J M Hayman, Jr, Howard T Karsner, A B Brower

Harley A Williams, Cleveland

Howard T Karsner, J M Hayman, Jr, A B Brower

Augustus Alonzo Hall, Columbus

J J Coons, John Dudley Dunham, A B Brower

Clovis Litle McKibben, Toledo

C W Waggoner, John T Murphy, A B Brower

PENNSYLVANIA

Louis Borsch Laplace, Philadelphia

David Riesman, Thomas M McMillan, E J G Beardsley

William Gilmore Leaman, Jr, Philadelphia

Robert G Torrey, Martha Tracy, E J G Beardsley

Edward W McCloskey, Philadelphia

Josephus T Ullom, T Grier Miller, E J G Beardsley

Edgar Schall Henry, Sewickley

Joseph H Barach, Samuel R Haythorn, E Bosworth McCready

SOUTH CAROLINA

James Albert Bradley, Florence

O B Mayer, J Heyward Gibbes, Kenneth M Lynch

TENNESSEE

Lucius Carl Sanders, Memphis

Conley H Sanford, Lyle Motley, J O Manier

VIRGINIA

William White Falkener, Newport News

Edward L Alexander, R Finley Gayle, Jr, J Morrison Hutcheson

Paul Douglas Camp, Richmond

Dean B Cole, R Finley Gayle, Jr, J Morrison Hutcheson

T Dewey Davis, Richmond

Dean B Cole, C M Caravati, J Morrison Hutcheson

Harry Walker, Richmond

William B Porter, Porter P Vinson, J Morrison Hutcheson

WASHINGTON

Robert Leonard King, Seattle

John M Blackford, G A Dowling, Charles E Watts

Frank Rowe Maddison, Tacoma

John M Blackford, Lester J Palmer, Charles E Watts

WEST VIRGINIA

James Lewis Blanton, Fairmont

C W Waddell, A H Stevens, Walter E Vest

Clement Coleman Fenton, Morgantown

Edward J Van Liere, G R Maxwell, Walter E Vest

CANADA

Manitoba

John McFaul McEachern, Winnipeg

J C Meakins, J Currie McMillan, Fred Cadham

Ontario

Frank Sparling Kennedy, London

F A Willis, A R Barnes, Jabez H Elliott

Candidates

Sponsors

	<i>Quebec</i>	
David William McKechnie, Montreal	R H M Hardisty, A T Henderson, D Sclater Lewis	
Harold Nathan Segall, Montreal	Charles F Martin, I M Rabinowitch, D Sclater Lewis	

Resolved, that the following list of 14 be and herewith are elected to Fellowship in the American College of Physicians as of April 3, 1938

Alfred Roe Masten, Denver	COLORADO Lorenz W Frank, Paul J Connor, Gerald B Webb
Benjamin Horn, Bridgeport	CONNECTICUT Daniel P Griffin, Charles H Sprague, Francis G Blake
Samuel John Lang, Evanston	ILLINOIS Arthur E Mahle, Charles A Elliott, James G Carr
Louis Anthony Monte, New Orleans	LOUISIANA Ben R Heninger, Edgar Hull, J E Knighton
Everett R Deweese, Kansas City Ellis W Willhelmy, Kansas City	MISSOURI George H Hovie, Peter T Bohan, A C Griffith Ferdinand C Helwig, D D Stofer, A C Griffith
Johnson McGuire, Cincinnati Clarence Elton Hufford, Toledo	OHIO William L Freyhof, John H Skavlem, A B Brower L A Levison, C W Waggoner, A B Brower
Bernard Isaac Comroe, Philadelphia	PENNSYLVANIA Simon S Leopold, Charles C Wolferth, E J G Beardsley
Robert Wilson, Jr , Charleston	SOUTH CAROLINA Hillyer Rudisill, Jr , Francis B Johnson, Kenneth M Lynch
Richard Edward Ching, Memphis	TENNESSEE J B McElroy, William C Chaney, J O Manier
Walter Belknap Whiting, Wichita Falls	TEXAS Henry A Christian, O B Kiel, C T Stone
Fuller Brvan Bailey, Salt Lake City	UTAH G G Richards, O J LaBarge, L E Viko
Arthur Lee Osterman, Wheeling	WEST VIRGINIA D A MacGregor, William M Sheppe, Walter E Vest

Resolved, that the following list of 148 be and herewith are elected to Associateship in the American College of Physicians

*Candidates**Sponsors*~~ALABAMA~~

Maurice James Abrams, Brewton
 James O Finney Gadsden
 David Barrow Snelling, Montgomery

~~J Harold Watkins, William H Smith, Fred Wilkerson
 Hugh J Morgan, John B Youmans, Fred Wilkerson
 J Harold Watkins, Seale Harris, Fred Wilkerson~~

ARIZONA

Donald Frederick Hill, Tucson

W Paul Holbrook, John W Gray, W Warner Watkins

ARKANSAS

John Nye Compton, Little Rock

John R Dibrell, Charles H Lutterloh, Oliver C Melson

CALIFORNIA

Clarence Wilmott Olsen, Los Angeles
 Fletcher Brandon Taylor, Oakland

Newton Evans, Percy T Magan, James F Churchill
 Thomas C McCleave, William H Strietmann,
 Ernest H Falconer

Rufus Anton Schneiders, San Diego

Lyell C Kinney, C Ray Lounsberry, James F Churchill

Hildahl I Burtness, Santa Barbara

W D Sansum, P A Gray, James F Churchill

COLORADO

Gerald Robert Fisher, Colorado Springs
 John Leonard McDonald, Colorado Springs

John A Sevier, J H Brown, Gerald B Webb
 John A Sevier, G Burton Gilbert, Gerald B Webb

CONNECTICUT

Curtis Tuttle Prout, Hartford

C C Burlingame, O G Wiedman, George Blumer,
 Francis G Blake

George Adolph Wulp, Hartford

John A Wentworth, J E Hutchison, Francis G Blake

David Jerome Cohen, Meriden

Thomas P Murdock, William E Hall, Francis G Blake

Harold Strickland, Meriden

Thomas P Murdock, William E Hall, Francis G Blake

William H Resnik, Stamford

Chester S Keefer, A R Felty, Francis G Blake

MEDICAL CORPS, U S NAVY

James Gillespie Dickson, Washington, D C

P F Dickens, Walter A Bloedorn, Dallas G Sutton

Bartholomew William Hogan, Washington, D C

C S Butler, C W Ross, Dallas G Sutton

Julian Love, Brooklyn, N Y

C S Butler, C W Ross, Dallas G Sutton

William Peter Mull Washington, D C

C R Baker, G E Thomas, Dallas G Sutton

Walter Johnson Pennell, Philadelphia, Pa

J B Helm, Joel J White, Dallas G Sutton

Earl Richison, Newport, R I

Joel J White, Otis Wildman, Dallas G Sutton

DISTRICT OF COLUMBIA

Alva Duckett Doughton, Washington

Lewis C Ecker, Janvier W Lindsay, Wallace M Yater

Leon Stuart Gordon, Washington

Thomas Czigas, William Gerry Morgan, Wallace M Yater

*Candidates**Sponsors*

Hugh Hudson Hussey, Jr , Washington

M. W. Perry, Thomas S Lee, Wallace M Yater

FLORIDA

Theodore Ferdinand Hahn, Jr , DeLand

Meredith Mallory, R H McGinnis, T Z Cason

Fred Mathers, Gainesville

George L Cook, R H McGinnis, T Z Cason

Albert Benjamin McCreary, Jacksonville

Louie Limbaugh, L B McBrayer, T Z Cason

GEORGIA

Evert Abram Bancker, Jr , Atlanta

Trimble Johnson, Hal M Davison, Glenville Giddings

Albert W Lewis, Jr , Atlanta

Russell H Oppenheimer, John B Fitts, Glenville Giddings

Joseph Carey Massee, Atlanta

Hal M Davison, Trimble Johnson, Glenville Giddings

John Warrick Thomas, Augusta

V P Sydenstricker, Eugene E Murphey, Glenville Giddings

William Edward Storey, Columbus

H Cliff Sauls, John B Fitts, Glenville Giddings

IDAHO

Samuel Marshall Poindexter, Boise

Clvde R Jensen, Cassius H Hofrichter, Charles E Watts

ILLINOIS

Clarence Lucas Gardner, Jr , Aurora

LeRov H Sloan, Joseph L Miller (deceased), James G Carr

James Alexander Walsh, Peoria

Orville Barbour, Fred M Mevner, James G Carr

Preston Vine Dilts, Pittsfield

Warren F Pearce, Harold Swanberg, Samuel E Munson

William J Bryan, Rockford

G B Lemmon, Leslie R Webb, A C Griffith

KANSAS

Norman Reider, Topeka

William C Menninger, Ralph M Fellows, Thomas T Holt

KENTUCKY

Ben Harvey Hollis, Louisville

Frank M Stites, J Murray Kinsman, C W Dowden

Arthur Trimble Hurst, Louisville

Virgil E Simpson, Sam A Overstreet, C W Dowden

John Stites, Louisville

William E Gardner, Arthur Clayton McCarty, C W Dowden

LOUISIANA

Lang Floyd Holland, New Orleans

Edgar Hull, J H Musser, J E Knighton

MARYLAND

Conrad Acton, Baltimore

William S Love, Jr , Paul W Clough, Henry M Thomas, Jr

MASSACHUSETTS

Walter Swan Burrage, Boston

Robert S Palmer, F Dennette Adams, William B Breed

Robert Titus Phillips, Boston

Louis M Spear, John W Dewis, William B Breed

Candidates

Thomas Van Orden Urmey, Boston

Lester Dow Watson, Milton

Joseph Victor Breen, Pittsfield

Sponsors

Ches⁷⁵ M Jones, Donald S King, William B
Breed
William D Reid, Herman C Petterson, William B
Breed
James Z Naurison, Paul D White, William B
Breed

MICHIGAN

Bergein Marion Overholt, Battle Creek

Robert Johnson Needles, Detroit

Louis J Steiner, Detroit

William Edward Jahnsman, Ferndale

M A Mortensen, Charles E Stewart, Henry R
Carstens
F Janney Smith, Frank R Menagh, Henry R
Carstens
Frank J Sladen, John G Mateer, Henry R Carstens
Robert H Durham, Frank R Menagh, Henry R
Carstens

MINNESOTA

Phillip Hallock, Minneapolis

Arthur C Kerkhof, Minneapolis

Benjamin Bismark Blum, Rochester

Hugh Roland Butt, Rochester

Eric MacMillan Chew, Rochester

Charles Douglas Deeds, Rochester

William Roland Gibson, Rochester

Donald W Ingham, Rochester

Walter Frederick Kvale, Rochester

Ferrall Harmon Moore, Rochester

Jay Conger Davis, Henry L Ulrich, E L Tuohy
S Marx White, Moses Barron, E L Tuohy
J A Bagen, Albert M Snell, E L Tuohy
Walter M Boothby, H Z Giffin, E L Tuohy
E V Allen, F W Gaarde, E L Tuohy
A R Barnes, H L Smith, E L Tuohy
Albert M Snell, James F Weir, E L Tuohy
F A Willius, A R Barnes, E L Tuohy
E V Allen, F W Gaarde, E L Tuohy
Nelson W Barker, Edgar A Hines, Jr, E L Tuohy

MISSOURI

Robert Emmet Britt, St Louis

David B Flavan, St Louis

Ralph A Kinsella, Charles Hugh Neilson, David P
Barr, A C Griffith
J Curtis Lyter, H W Soper, A C Griffith

MONTANA

Wavne Gordon, Billings

W G Richards, Edward J Stieglitz, Louis H
Fligman

NEBRASKA

Esley Joseph Kirk, Omaha

Ernest Lynn MacQuiddy, Omaha

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Dr. Sydney R. Miller proceeded with his report "The Committee on Credentials has reviewed 4 applications for reinstatement, and, after due consideration, moves the adoption of the following resolution

"*Resolved*, that in accordance with the rules and regulations governing reinstatement, the following be and herewith are reinstated as Fellows of the American College of Physicians—Dr. Clarence Henry Beecher, Burlington, Vt., Dr. Gilbert E. Brereton, Dallas, Tex., Dr. William H. Stewart, New York, N. Y., and Dr. Julius Ullman, Buffalo, N. Y.

"The motion was seconded by Dr. Charles H. Cocke, and unanimously carried."

Dr. George Morris Piersol, Chairman of the Committee on Advertisements and Commercial Exhibits, reported as follows "This Committee, after due consideration, has drawn up certain fundamental principles that they recommend for adoption to govern the College in the matter of exhibitors at the Annual Convention, namely

"(1) Exhibitors shall be admitted on invitation only,

"(2) The initial approved 'Invitation List' shall be made up by the Committee and the Executive Secretary. Both the firm and the product must be approved

Preference shall be given to exhibits of a scientific nature, such as pharmaceuticals, equipment and medical books,

"(3) Additions to the initial approved 'Invitation List' may be made by the Committee after application by firms, with the requirement that they submit complete literature concerning their products and their organization

"(4) The 'Invitation List' may be revised annually on the recommendation of the Committee"

Dr Piersol said that if such rules are adopted, it will give the Executive Secretary ample latitude in the regulation of exhibitors and in the exclusion of exhibits irrelevant to the practice of Internal Medicine or one of its allied specialties

On motion by Dr James E Paullin, seconded by Dr Roger I Lee, and unanimously carried, it was

Resolved, that the recommendations of the Committee on Advertisements and Commercial Exhibits be approved

Dr Maurice C Pincoffs, Chairman of the Committee on Revolving Loan Fund, reported as follows "The Committee on Revolving Loan Fund, at a special meeting, has discussed in detail a project which we would like to submit at this time not for adoption, but for approval in principle, feeling that if it is thus approved, it will merit going into the laborious task of reducing it to a form where it could be considered and adopted at a later meeting The Committee feels that the principle of establishing a Revolving Loan Fund is justified, because the College has added to the difficulties of young men preparing themselves for Internal Medicine, and there is danger that those difficulties may keep from Internal Medicine valuable men, both in character and ability It is especially fitting, therefore, that the College should, within its means, attempt to aid that group of unknown size who may otherwise be deterred from going into Internal Medicine We feel that we should attempt to aid them only insofar as we have or shall have added to their obstacles In other words, if we consider, in a rough way, that we have added about two years to the average term of preparation, we should not attempt to carry a man through the whole period of training of five years, but only through the two additional years for which we have been responsible It is also advisable because any longer period complicates the economics of the plan, and will be an undue burden of debt upon any young man who would wish to take advantage of it The mechanism for putting the Loan Fund into effect is that this Board, or the President, as may be deemed advisable appoint in each Class A medical school a representative from among those Fellows or Officers of the College that are attached to that school who will assume the burden of forming his local committee to receive applications for aid from young men, either during their graduate work in that school or in that territory in other institutions The filling out of blanks carefully, looking into the character and ability of the applicant and into his needs would fall upon each local committee The application then should come to the standing committee, analogous somewhat to the Committee on Credentials A standing committee of that type should meet semi-annually to consider applications coming from the different sections of the country, and pass upon them both in relation to their merit and to the funds available

"Some preliminary study has been made of the question of funds and the manner in which a Revolving Loan Fund works (Dr Pincoffs thereafter passed around a chart) To make it specific, a project has been worked out for four men, two for two years at \$1,000 00 a year each, and two for two years at \$500 00 a year each This would entail an expenditure over a period of eleven years before the Fund would first become self-supporting of somewhere around \$3,500 00 a year average After eleven years it would become somewhat better than self-supporting, and if at any time it should stop, the payments going on would pay back to the College in the course of another eleven years what had been put into it

"It would be possible, with a sum approximating \$8,000 00 a year, to run units of a minimum of sixteen men. I say 'a minimum' because that figure of sixteen is based on our giving the maximum aid to each man, whereas it would be our endeavor to give such aid as should be urgently needed. ~~probably the number aided would be far in excess of sixteen. I may say that this is felt to be in the nature of an experiment.~~ I have consulted the Harmon Foundation, which has had a rather extensive experience in student loan work. As far as it is aware, there has been no loan fund of exactly this kind for graduate medical men, although some graduate medical men have received loans from funds devised for general aid for students. Our suggestion is in the nature of an experiment, which the College can cut short within a year, because the loans only extend over two years and the maximum amount is never such as would be crippling, and the yearly outlay, we feel, whether we start with \$4,000 00 or \$8,000 00, is something that our recent surplus could afford. The Committee feels that a more detailed plan in writing should be submitted to the Regents. The Committee, however, presents this interim report and hopes that the suggestion may be approved, if it seems feasible, or the plan discarded before any further work is put on it.

The College has been instrumental in adding to the requirements for entering Internal Medicine by raising its standards of admission to Fellowship and by initiating the American Board of Internal Medicine. It is felt that men will often require aid in their last two years before coming up for certification. The plan is based on allowing two years after certification before any beginning of repayment is made. The sum arbitrarily set for them to pay is at the rate of \$20 00 a month, or \$240 00 a year, which in the smaller loans enables them to make full repayment in a little over five years, and in the maximum loan, enables them to make repayment in ten years. It would never exceed ten years, and the Committee feels that it would often be under five."

There was general discussion of the report, with some consideration of the possibility of losses. From the experience of other loan funds, losses have been negligible, arising mainly due to death.

On motion by Dr. James Alex. Miller, seconded by Dr. James B. Herrick, and unanimously carried, it was

Resolved, that it be the sense of the meeting of the Board of Regents at the present time that the plan offers very interesting possibilities, and that the Committee be instructed to go ahead with the further details for the development of a completed plan.

Dr. David P. Barr, Chairman of the Committee on Fellowships and Awards, reported that the Committee had duly considered a number of names submitted as candidates for the John Phillips Medal. He read a list of the names of the men who had been considered, and discussed in particular the names of those who had been most seriously considered.

On motion by Dr. Barr, seconded by Dr. James E. Paullin, and unanimously carried, it was

Resolved, that the 1938 award of the John Phillips Memorial Medal be made to Dr. Harry Goldblatt, of Cleveland, Ohio, in recognition of his having devised an important method for the production and study of experimental hypertension in animals, for his having demonstrated the significance of renal ischemia in the causation of high blood pressure, and for his having contributed significantly to the understanding of essential hypertension, one of the most common and disabling conditions encountered in medical practice.

Dr. Barr proceeded with the second part of his Committee's report, in regard to a number of candidates considered by the Committee this year for the American College of Physicians' Research Fellowship. Only eight applications had been con-

sidered, and it was decided that the Committee would recommend only one Research Fellowship, this to be awarded to John Russell Smith, who, since his graduation, has served as Intern and Assistant Resident at the Barnes Hospital, St. Louis, and who has been engaged in research, most of the time, with Dr. W. B. Kuntz, in problems of circulation and respiration. His most recent work has been with Dr. Kuntz, conducting observations on peripheral vascular diseases. Dr. Smith desires to go to Professor Anrep in Egypt to pursue his studies, particularly of circulation and respiration.

On motion by Dr. Barr, seconded by Dr. W. D. Stroud, and unanimously carried, it was

Resolved, that a Research Fellowship in the amount of \$1,800.00 for 1938-39, beginning July, 1938, be awarded to Dr. John Russell Smith.

Dr. Barr reported that it was the hope of the Committee that in not presenting a candidate for the second Research Fellowship for 1938-39 that the fund may be so earmarked that the following year, given suitable candidates, the Committee might recommend three men instead of two.

Dr. O. H. Perry Pepper made the suggestion that the Committee consider doing something to find positions for the recipients of fellowships after the period of fellowship has expired. Dr. Barr was in agreement with this suggestion.

On motion by Dr. Barr, seconded by Dr. Jonathan C. Meakins, and unanimously carried, it was

Resolved, that the fund of \$1,800.00 not expended for 1938-39 for a second Research Fellowship be, nevertheless, appropriated for use for a third Fellowship during 1939-40, if desirable.

On motion by Dr. Barr, seconded by Dr. James E. Paullin, and unanimously carried it was

Resolved, that the College shall place at the disposal of each recipient of a Research Fellowship any part of the fund which the recipient may need at the beginning of his fellowship, so that it may be used for necessary expenditures in transportation, etc., subject to the recommendation of the Committee.

Dr. James Alex. Miller, Chairman, reported for the Committee on Future Policy for the Development of Internal Medicine.

"(1) The Committee recommends that the Regents request the Executive Secretary to look into the matter of liability insurance for members of the College from various angles and report to the Committee."

On motion by Dr. Miller, seconded by Dr. O. H. Perry Pepper, and unanimously carried, it was

Resolved, that the above recommendation be carried out.

"(2) The Committee recommends that the Board of Regents appoint a special committee to study the matter of graduate education in cooperation with the American College of Surgeons. Also, that the Regents consider the possibility of creating a standing committee on graduate education."

There was some discussion of this subject, Dr. Pincoffs spoke in favor of the idea of having a standing committee created, not necessarily of the Regents alone, but one including any member of the College particularly valuable for such work. Dr. James D. Bruce said that he would very strongly recommend that a committee of "this body be named, which can and may collaborate with the various national committees when and if their advice and assistance may be called for."

On motion by Dr. James Alex. Miller, seconded by Dr. Walter L. Bierring, and unanimously carried, it was

Resolved, that the Board of Regents authorize the appointment of a committee by the President of a size which he may select, not necessarily confined to members

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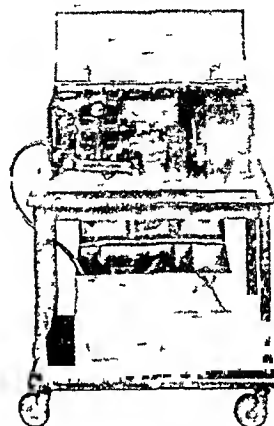
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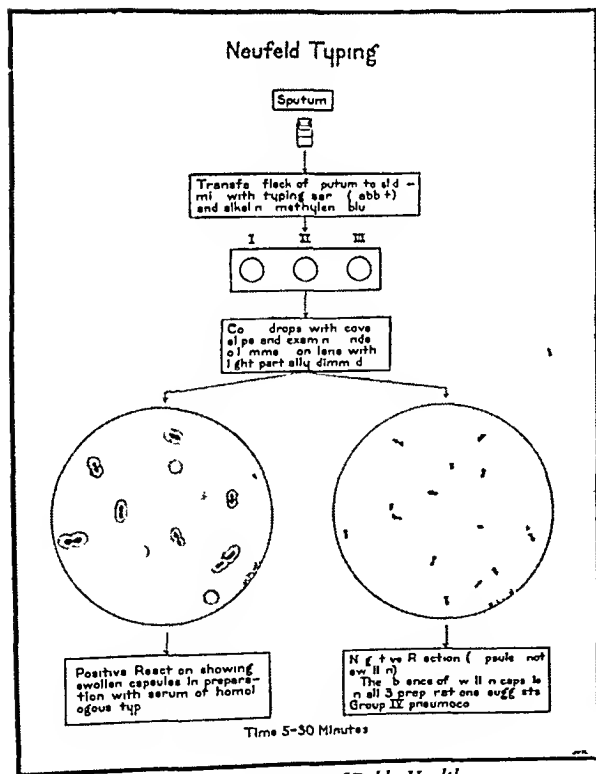
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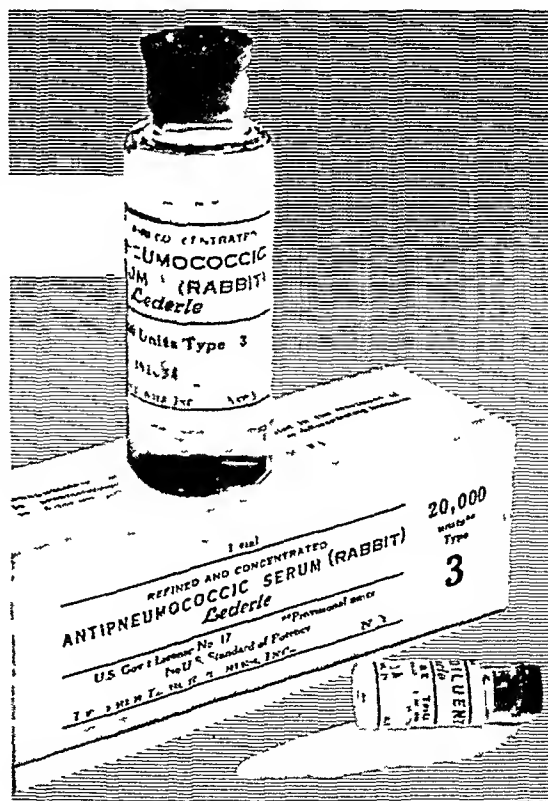
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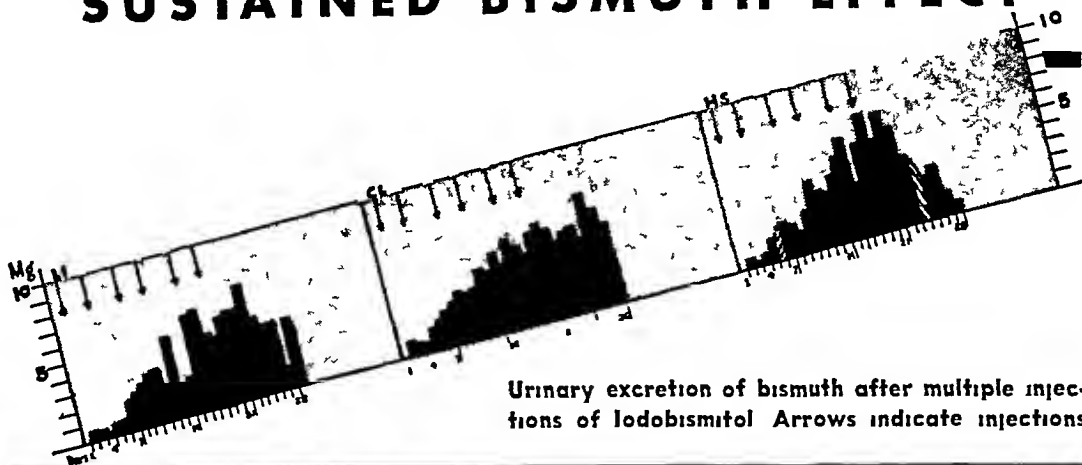
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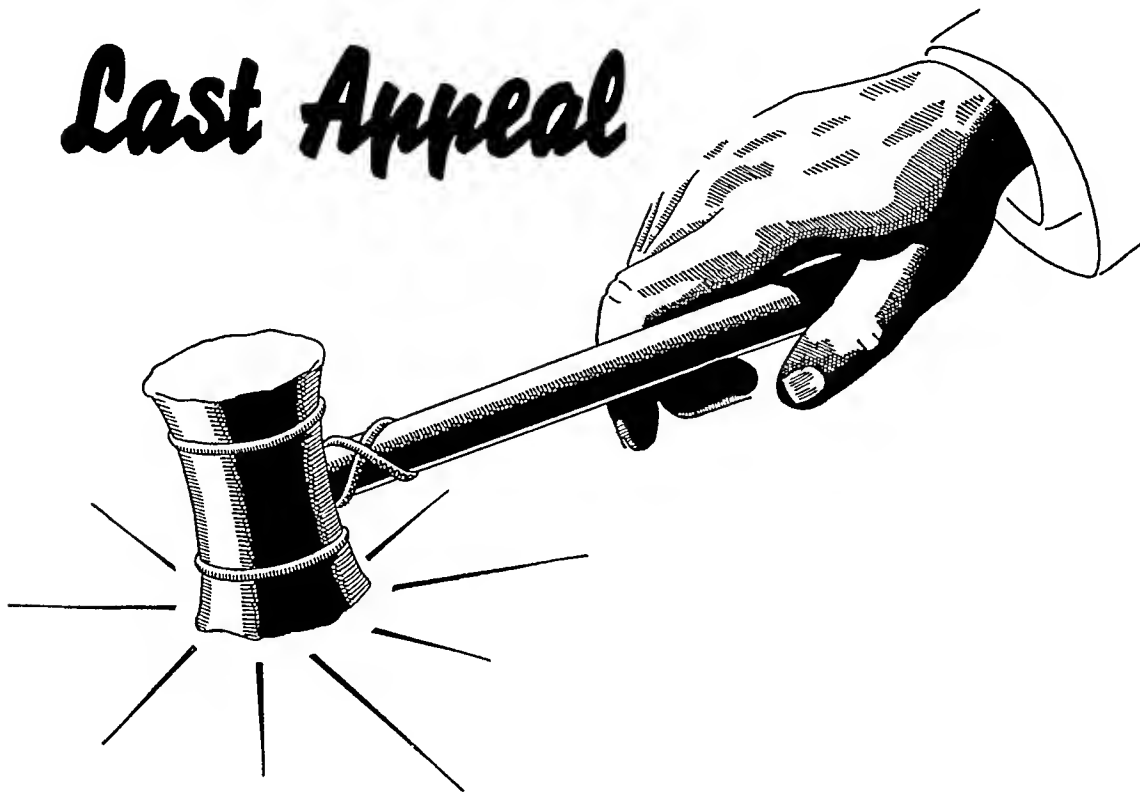
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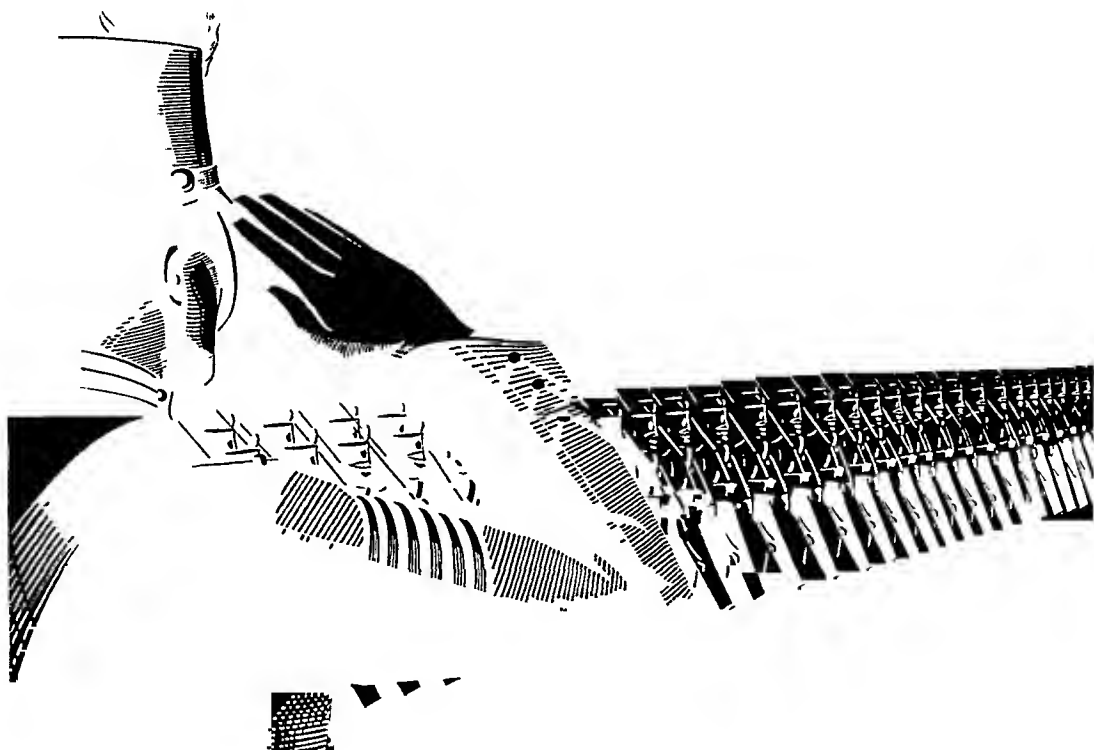
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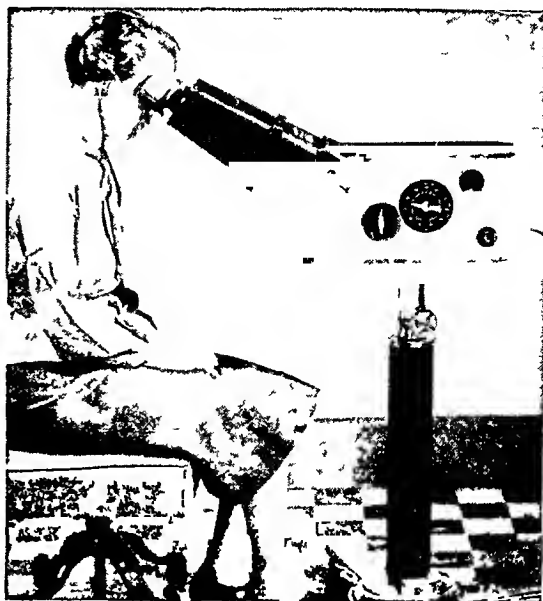
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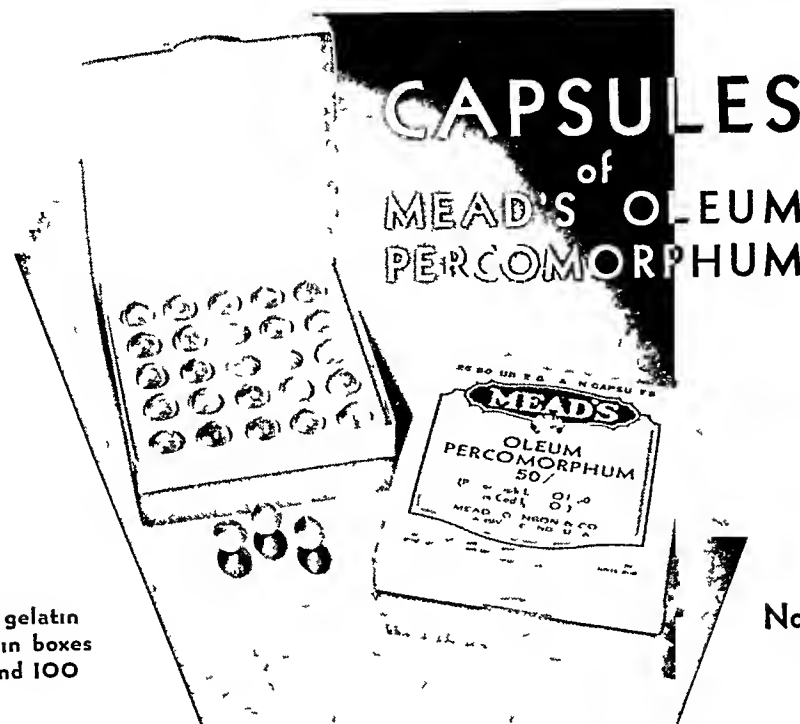
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ANNALS OF INTERNAL MEDICINE

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NUMBER 8

THE IMPORTANCE OF OCULAR SIGNS IN THE DIAGNOSIS OF BRAIN TUMOR

By ERNEST SACHS, M D , *St Louis, Missouri*

ORDINARILY, when discussing the diagnosis of brain tumors, one passes in review more or less completely the whole gamut of diagnostic signs and symptoms. But in this paper I propose to select only one small part of the nervous system—the eyes—and try to show how it may be possible to localize a lesion in almost any part of the brain if the study of this part be sufficiently thorough.

The eyes should be studied from five angles

- I Ocular palsies
- II Ocular movements
- III Visual defects
- IV Ophthalmoscopic changes
- V Subjective visual disturbances

I Ocular Palsies The nerve most frequently affected by a brain tumor is the sixth nerve. This is due to the fact that it has such a very long course in the cranial cavity, and also because it may be compressed as it leaves the pons by one of the branches of the basilar artery. As the pressure on the nerve may vary from day to day, or even from hour to hour, the patient's ability to turn the eye outward will also vary. Such a sixth nerve paresis is usually unilateral. It is of no localizing value and must be considered a sign of general pressure.

On the other hand, a bilateral sixth nerve paralysis, inability to look to either side, is of great significance because in my experience it always means a lesion of the medulla where the two sixth nerves have their origin.

When the oculomotor nerve, the third, is thrown out of function, the pupil is dilated, and the eye can be moved only outward and downward. This striking picture, when it occurs suddenly, not only indicates where the lesion is but what it is, namely, an aneurysm of the internal carotid where it enters the circle of Willis. Such cases may have no other symptom.

* Read at the St. Louis meeting of the American College of Physicians, April 20, 1937

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than headache, the eye grounds remain normal, there is no choked disc. If, however, a third nerve paralysis develops somewhat slowly, and is combined with a choked disc, we must conclude that we are dealing with a tumor in that region, the favorite site of which is just in front of the carotid at the sphenoidal fissure. The tumors at this point have their origin from the meninges and are meningiomas, one of the most satisfactory types of brain tumor which we are called upon to treat. But mere dilatation of the pupil, without any involvement of the other muscles supplied by the third nerve, is of entirely different significance. When that happens, only the sympathetic fibers are involved. One sees this in apoplectic conditions and especially in head injuries. Such dilatation is a grave prognostic sign, and usually means a lesion, most often a hemorrhage, in or near the lateral ventricle of the same side.

II Ocular Movements The disturbances of ocular movements are the various types of nystagmus. Lateral nystagmus, when the to and fro movement is equally rapid, may be due to a congenital lesion or to multiple sclerosis, but when there is a rapid component to one side with a slower recovery, then there is a disturbance of the vestibular mechanism, and if the patient has other signs of a tumor we may be quite certain that the nystagmus is caused by an irritative lesion in one of the lateral lobes of the cerebellum,—in the right lobe if the nystagmus is more marked to the right, and in the left lobe if it is more to the left.

Vertical nystagmus is a very different affair. Not only is it produced in quite a different way but it is of considerable prognostic value, which cannot be said of lateral nystagmus. It is a much graver sign than lateral nystagmus because it is produced by an *irritative* lesion far forward in the posterior cranial fossa and is evidence that the lesion, almost invariably a tumor, is pressing upon the corpora quadrigemina. These tumors lie in the median line in the fourth ventricle, and usually are medulloblastomas which are very radio-sensitive. But if a patient is unable to turn his eyes upward, we may be sure that we are dealing with a *destructive* lesion of the corpora quadrigemina and not an irritative lesion of that area. Such lesions, some of them pineal tumors, usually lie in the posterior portion of the third ventricle which but a few years ago was a "noli me tangere" for the neurological surgeon. Today, however, in every large neurosurgical clinic, a number of such tumors have been successfully removed.

As a rule, the absence of a symptom is not of diagnostic value, yet the absence of nystagmus may at times be of very great significance. If a patient presents all the cardinal symptoms of a cerebellar lesion, but has no nystagmus, it means either that the lesion is on the surface of the lateral lobe of the cerebellum and has not involved the nuclei of the cerebellum, or that the lesion is in the region of the middle lobe, the vermis, well away from the lateral cerebellar nuclei which control the lateral eye movements.

I shall merely mention in passing the conjugate movement of the eyes

to one side, which is sometimes confused with nystagmus, but which has its origin in a center in the frontal lobe, and the mistaking of cerebellar tumors for frontal lobe tumors in the past was probably due in part to the misinterpretation of this symptom

I cannot leave this phase of the subject without drawing attention to unilateral exophthalmos, caused by a meningioma growing from the olfactory groove, which occurs often without any other signs of an intracranial tumor and occasionally in orbito-ethmoidal osteomata. Nor can I omit mention of that extraordinary phenomenon, pulsating exophthalmos, due either to an arteriovenous aneurysm or to a vascular tumor behind the orbit

III Visual Defects The optic nerves and their cerebral connections extend from the under surface of the brain in the anterior fossa to the posterior portion of the middle fossa. Lesions in the course of the visual pathway may produce different kinds of field defects, and by these field defects alone it may be possible to locate a lesion quite accurately. These defects may consist of scotomata, central or paracentral, partial or complete bitemporal hemianopsia, partial or complete homonymous hemianopsia.

A lesion that presses directly on the optic nerve may produce a primary optic atrophy and associated with this a central or paracentral scotoma. A lesion in the orbit or an intracranial lesion in the anterior fossa in front of the chiasm may produce unilateral optic atrophy. If the process has been present for a long time, the patient may lose the sight of one eye completely. We have seen this a number of times in tumors of the pituitary gland. In the series of 78 cases of pituitary tumors and suprasellar cysts which we have operated upon, blindness in one eye occurred 28 times, 18 times in the pituitary tumor cases and 10 times in the cases of suprasellar cysts. There may also be unilateral blindness caused by primary optic atrophy associated with a choked disc in the opposite eye,—that interesting but rather rare syndrome described by Foster Kennedy. This means that there is a lesion on the under surface of the frontal lobe on the side of the optic atrophy. The tumor pressing directly on the nerve causes the atrophy and by causing increased intracranial pressure produces a choked disc in the opposite eye. The eye disturbance associated with a pituitary tumor is practically always a primary optic atrophy. Only in those very rare cases in which a pituitary tumor perforates the dural envelope which roofs the sella turcica, and hence becomes intradural, does one see a choked disc. This has occurred only once or twice in our series.

The characteristic field defect produced by a pituitary tumor is bitemporal hemianopsia and this is unaccompanied by choked disc. In an early case, the bitemporal defect may be detected only in the color fields. A pituitary tumor, however, may grow out to one side and then produce an homonymous hemianopsia. Such a field defect is indistinguishable from that produced by an occipital lobe lesion, but if the tumor is in the occipital

lobe there will almost certainly be double choked disc, while the pituitary case will have only a primary optic atrophy and characteristic roentgen-ray changes in the sella

I have seen a few cases of hemorrhage into the occipital lobe, apoplexy of the occipital lobe, in which there was no choked disc, but in these cases the history of a sudden vascular insult will enable one to make the differential diagnosis

Some of the visual fibers, as they pass back toward the cuneus of the occipital lobe, make a loop in the temporal lobe, those fibers which pass to the outer side of the inferior horn of the lateral ventricle control vision in the upper outer quadrant, while those which pass to the mesial side of the ventricle control the lower outer quadrant. The nearer the lesion lies to the occipital lobe, the more nearly complete is the homonymous hemianopsia but the macular, or central vision, in an occipital lobe lesion is spared because the macula is bilaterally represented

The right temporal lobe, in a right-hand individual, was until recently considered a silent area of the brain, but these partial homonymous defects are so definite and so characteristic that they alone enable one to localize a lesion in the temporal lobe

To recognize these different types of field defects, it is essential that the examination be carried out with great care. A careless or hastily made perimetric study will not reveal such slight defects and vision must be tested every 15 degrees in order to detect these changes

Patients with such homonymous field defects often have peculiar subjective visual disturbances—hallucinations. The character of these hallucinations frequently will enable one to differentiate a temporal from an occipital lobe lesion

IV Ophthalmoscopic Changes The ophthalmoscopic study of the eye grounds is another aspect of the ocular mechanism that yields invaluable information. There are two general types of changes that one may observe. First, primary optic atrophy, and second, choked disc or papilledema

An intracranial, intradural tumor never causes bilateral primary optic atrophy. Consequently, we may conclude that if a patient has other evidence of an intracranial lesion and bilateral primary optic atrophy, the lesion must be extradural. The only intracranial lesions that produce this picture are situated around the chiasm. Most frequently these are pituitary tumors, aneurysms of the internal carotid, or an inflammatory process in that region. But of course it does not follow that because a patient has a primary optic atrophy the lesion is necessarily intracranial, for lesions in the orbit may also cause such atrophy. Since a variety of extracranial causes may produce such a picture, other diagnostic signs have to be taken into consideration before arriving at a final diagnosis

Choked disc is always due to increased intradural pressure. In the vast majority of cases the pathological lesion is a brain tumor and in these

cases the appearance of the choked disc offers many points of interest. First of all we must ask, can a choked disc be of any localizing value? It has been claimed that unilateral choked disc indicates the side on which the lesion is located. In my experience this is rarely the case, and unilateral choked disc, therefore, is of very little localizing value. Nor are the number of diopters of swelling of much importance. What we must be interested in is the age of the process, and this is best judged by the changes, histological in character, seen with the ophthalmoscope. The character of the hemorrhages, whether recent or old, and the presence of exudate, which is evidence that new tissue is being laid down in the retina, are the points to be looked for. The diopters of swelling, on the other hand, are merely evidence of the amount of edema, and this fluctuates so readily that it is of far less importance than the other changes.

The appearance of secondary optic atrophy in a choked disc is of great prognostic importance and with experience it is possible to recognize optic atrophy while a choked disc is still present. If optic atrophy is well advanced, the vision may continue to fail even if the choked disc has been relieved by the removal of a tumor, a patient may even go on to blindness in such a case.

The question has been raised, can a patient who is blind as a result of a choked disc ever regain any vision? I have never seen a patient, who has been blind even a brief time as a result of a choked disc, regain his vision, but I have seen several patients, blind because of a primary optic atrophy due to a pituitary tumor, regain normal vision. This I confess is difficult to explain, but I have assumed in such cases that we were dealing with a physiological block of the nerve.

There are a number of conditions which resemble a choked disc so closely that they are difficult to tell apart, and at times indistinguishable. In malignant hypertension, polycythemia, and true optic neuritis due to an inflammatory process, the picture is very similar. Even albuminuric retinitis at times may very closely resemble a choked disc. At times it may be possible to tell these apart only by considering other aspects of the clinical picture. In this connection I should like to emphasize that there still are points about the mechanism of choked disc that are not fully understood. There is some evidence indicating that the same mechanism may be producing the eye ground changes in several of these conditions. If this should prove to be correct, there would no longer be any justification for applying different names to these various eye ground conditions.

V Subjective Visual Disturbances The final group of visual disturbances which I want to refer to are the subjective ones. These are in the nature of hallucinations and may be grouped under two general headings—the hallucinations of form and those of color. An irritative lesion of a cortical center gives rise to these subjective sensations. The visual phenomena are different, depending upon the portion of the cortex that is in-

volved. As a rule, irritation of the visual center in the occipital lobe gives rise to hallucinations of color. The patient sees these colors in a certain portion of the perimetric field. Thus, for example, if the lesion is located in the right occipital lobe, the patient will see these colors in the left half of each visual field, since the right occipital lobe controls the vision in the right half of each retina. These colors are often described by the patient as coming from one side. In a right occipital lobe lesion they would therefore appear from the left side.

In a certain number of lesions of the temporal lobe, patients may have visual hallucinations of form. They may see peculiar things or persons. Individuals may appear deformed, they may see strange people or animals. Many of these hallucinations are very similar to those described by patients in delirium tremens, and it may be that alcohol affects the temporal lobe particularly, producing such symptoms. At times these visual disturbances may be very complicated. I recall one patient, a very intelligent school teacher, who always saw an Elizabethan pageant pass before her. She saw all this so vividly that she was able to describe the costumes accurately. This type of visual hallucination is closely allied, if not a part of, the irritative lesions produced in the temporal lobe, which were first described by Hughlings Jackson, and called by him "dreamy states." In these attacks the patient not only may see peculiar things but often also may hear strange voices, with all this he has a sense of unreality, not knowing where he is, and often forgetting his own identity.

These two types of visual hallucinations may constitute the auras preceding a Jacksonian convulsion. Associated with these visual disturbances there may often be field defects, and such a combination—visual aura, Jacksonian convulsion, and field defect—constitutes ample evidence on which to localize a lesion in the temporal or occipital lobe.

In trying to determine the location of a brain tumor, numerous methods need to be employed, but I have attempted only to point out the great importance of ocular signs and the significant rôle they play in the diagnosis of brain tumor.

THYROID ACTIVITY IN CHRONIC ARTHRITIS *

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OPINIONS differ as to the relationship between thyroid activity, as determined by the basal metabolic rate, and variations in the arthritic syndrome

The increased incidence of arthritis in women, particularly near the menopause, and the association of myxedema and hypothyroidism with chronic arthritis have suggested to many that a deficient thyroid secretion might be a contributing factor in the production of arthritis. Pemberton and Tompkins¹ studied the basal metabolism of 29 cases and found the basal metabolic rate (B M R) within normal limits (between plus and minus 10) in 80 per cent, the remainder being below normal. Cecil, Barr and DuBois² studied four patients with chronic arthritis in a calorimeter and concluded that there was no disturbance of metabolism. Boothby and Sandiford^{3,4} found the B M R between plus and minus 15 in 93 per cent of 69 patients with chronic arthritis. In 115 cases studied by Hench⁵ the B M R was normal in 80 per cent. Swaim^{6,7} reported a total of 312 cases. The B M R was normal in 61 per cent, below normal in 25 per cent (below 0 in 63 per cent), and above normal in 14 per cent. He concluded that "abnormal metabolism with a tendency to a minus rate is characteristic of arthritis, especially in early years, having a tendency to return to normal as the duration of the disease lengthens". Hall and Monroe⁸ reported that, in 214 cases of which 106 were rheumatoid and 108 osteoarthritis, the B M R was normal in 48 per cent and below normal in 43 per cent. However, the B M R was below 0 in 75 per cent of the cases. Hence it would appear from the latter reports that the B M R falls within accepted normal limits in the majority of patients with chronic arthritis, although most of the rates are below 0.

Hall and Monroe⁸ have discussed the literature on the relation of endocrine dysfunction to arthritis.

The present study was undertaken to determine particularly (a) the frequency distribution of the B M R in patients with chronic arthritis, (b) whether any particular range of B M R is characteristic of any one type of arthritis, (c) the relation between the B M R and disease activity, as indicated by the sedimentation rate and non-filament cell count, (d) the relation between the duration of the disease and the B M R, and (e) the effect of the administration of thyroid extract upon the course of the disease.

A total of 684 B M R determinations was made on 400 patients se-

* Received for publication March 25, 1937

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lected without discrimination on admission to the clinic. In those cases in which the results were checked, the lowest figure was considered correct.

The relationship between the B M R and activity of the disease was studied by making serial tests during the course of treatment. The sedimentation rate and non-filament cell count were done simultaneously with the B M R determination. Rates between plus and minus 10 were considered normal.

TABLE I
Distribution of Basal Metabolic Rates in 400 Patients with Chronic Arthritis

Type of arthritis	Sex	Number of cases	Basal metabolic rates							
			% +31 to +40	% +21 to +30	% +11 to +20	% 0 to +10	% 0 to -10	% -11 to -20	% -21 to -30	% -31 to -40
Rheumatoid	M	48		2.1	8.3	16.7	29.2	37.5	6.2	
	F	93	6.4	8.6	14.0	25.7	30.0	10.8	4.3	
Mixed	M	32		6.0	3.1	6.0	59.5	21.9	3.1	
	F	111	0.9	0.9	13.5	29.8	32.5	15.2	6.3	0.9
Osteo	M	42		2.4	9.5	14.6	45.3	19.0	9.5	
	F	74		5.4	8.1	33.8	28.7	17.6	2.7	2.7

FREQUENCY DISTRIBUTION OF BASAL METABOLIC RATES

Table 1 shows the distribution of B M R in the different types of arthritis. The rates were normal in 59 per cent, below normal in 24.3 per cent (below 0 in 58 per cent), and above normal in 16.7 per cent of all cases, which agrees with the proportions found by Swaim^{6,7}. The distribution of B M R was essentially similar in the different types of arthritis, except that there were more cases with B M R above normal in the rheumatoid group.

In 141 patients with rheumatoid arthritis, the B M R was above normal in 22.6 per cent, normal in 52.5 per cent, and below normal in 24.9 per cent.

In 143 patients with mixed arthritis, the B M R was above normal in 13.2 per cent, normal in 63.8 per cent, and below normal in 23.0 per cent.

In 116 patients with osteo-arthritis, the B M R was above normal in 12.0 per cent, normal in 63.0 per cent, and below normal in 25.0 per cent.

RELATION BETWEEN THE BASAL METABOLIC RATE AND ACTIVITY AND DURATION OF THE DISEASE

In table 2, the mean sedimentation rate (Westergren method), non-filament cell count, and duration of the disease in months are arranged ac-

TABLE II

Comparison of the Basal Metabolic Rate with the Sedimentation Rate, Non Filament Cell Count and Duration of the Arthritic Disease

Findings compared	Type of arthritis	Basal metabolic rate									
		+31 to +40	+21 to +30	+11 to +20	0 to +10	0 to -10	-11 to -20	-21 to -30	-31 to -40	Mean +10 and above	Mean -10 and below
Number of tests	Rheumatoid	7	14	25	50	66	38	10			
	Mixed	1	4	26	50	75	34	8			
	Osteo		5	11	34	43	22	6	2		
Mean duration of disease in months	Rheumatoid	43	60	53	41	44	54	43		55.4	49.7
	Mixed	17	88	10	64	91	76	103		93.9	76.4
	Osteo		69	64	44	44	77	37	69	65.7	57.3
Mean sedimentation rate	Rheumatoid	30	35	34	25	28	23	17		33.8	19.9
	Mixed	38	10	22	19	24	19	15		23.0	16.7
	Osteo		7	9	19	23	21	10	14	14.4	11.2
Mean non-filament cell count	Rheumatoid	21	23	18	15	18	14	11		19.0	13.3
	Mixed	9	11	16	14	24	13	13		14.8	12.7
	Osteo		10	15	15	17	15	11	16	13.5	11.7

according to the type of arthritis and the B M R. On the basis of 527 tests made on 341 patients, the following relationships were found. The sedimentation rate, non-filament cell count and duration of disease were higher in all groups with basal metabolic rates above normal. This was particularly true of patients with rheumatoid arthritis, the mean sedimentation rate being 33.8 mm in the above normal group and 19.9 mm in the below normal group and the mean non-filament cell count being 19.0 in the above normal group and 13.3 in the below normal group.

EFFECT OF THE ADMINISTRATION OF THYROID EXTRACT

Thyroid extract (Lilly) was administered to a number of patients with chronic arthritis, with the following results. Only 20 per cent of patients with markedly active rheumatoid arthritis showed improvement. Many patients could tolerate only small doses and, in some instances, it was necessary to discontinue it. In other patients there was increased resistance to intercurrent infection, the appetite improved and there was a sense of well-being. However, both the joint symptoms and the B M R remained unaffected in these cases, even though the latter was below normal.

A number of patients who had shown marked hypersensitivity to vaccine tolerated larger doses and the arthritis improved when thyroid extract was also given. Patients who did not respond to thyroid extract alone improved when given vaccine also. Thus thyroid extract is a valuable adjunct in some cases, but it does not always bring about improvement when used alone.

About 41 per cent of patients with mixed and osteo-arthritis improved

following the administration of thyroid extract. This was particularly true in those cases involving the knee joints. Overweight women with large, swollen, tender, painful, stiff knees often had excellent results, particularly in reduction of swelling, increased motion and lessened pain. When the fingers were involved, marked improvement was often noted, particularly in early cases. Osteo-arthritis of the hip, spine or shoulders did not respond to the administration of thyroid extract, but good results frequently followed its use in inactive cases of the Marie Strumpell type of arthritis. The B M R frequently became normal in patients with mixed and osteo-arthritis, but rheumatoid types were influenced only infrequently.

DISCUSSION

The results obtained in the 400 cases reported in this paper confirm the reports of previous workers, that the basal metabolic rate is below 0 in 55 to 80 per cent of patients with chronic arthritis.

The smaller number of B M R below normal in the present series of cases as compared with those reported by Hall and Monroe⁸ may be explained, as they pointed out, by several factors. For example, ambulatory patients, such as those studied in the present series, have higher B M R than hospital patients. Further, constant pain, causing insufficient rest and sleep, increased nervousness, etc., all tend to increase the B M R. This lends support to the contention of Hall and Monroe⁸ that the calculated B M R in these patients is always higher than the true rate. Assuming that the calculated rates were about 10 per cent too high, and adjusting the observed rates by this correction, 82 per cent of the patients in the present series will be found to have a B M R below 0.

Poor nutrition of the joint has long been considered a causative factor in hypertrophic arthritis and, for that reason, this type of arthritis has been referred to as "degenerative" or "senile." The occurrence of several signs of hypothyroidism in patients with osteo-arthritis led Hall and Monroe⁸ to believe that a lack of thyroid secretion was a factor in the etiology of these cases. Swain⁶ suggested that a low B M R may precede arthritis. It is quite possible that a decreased secretion of thyroid hormone may affect the nutrition of the joints. Osteo-arthritis may also result from long-continued inadequate repair of traumatized joints. This theory is supported by the fact that joints, such as those of the hips, spine, knees and fingers, which are subject to considerable mechanical stress and strain are most frequently involved in hypertrophic arthritis. However, this theory may not apply to rheumatoid arthritis, in which case infection probably plays a prominent rôle and lowered metabolism is only one of a long chain of effects.

The B M R is increased in the active stage of early rheumatoid arthritis, but is reduced when the disease becomes chronic, even though signs of active infection may still persist. As the disease becomes less active and ankylosis begins to develop, the B M R tends to return to normal.

In the chronic stage, the brunt of the toxemia falls upon the liver, producing symptoms of intoxication of that organ in addition to those already affecting the thyroid. Usually there is also anemia, loss of weight, nervousness, emotional instability, rapid pulse, poor appetite, etc. In studies made in this clinic,⁹ 73 per cent of such patients had liver dysfunction as judged by the Azorubin S appearance time. We⁹ have confirmed Davis'¹⁰ findings that the majority of these patients have lowered serum proteins and a reversal of the serum albumin-globulin ratio. The B M R was below normal in 90 per cent of patients with abnormal Azorubin S appearance times and altered albumin-globulin ratios.

In the ankylosing stage the improved B M R can be explained by lessened toxemia which permits the liver and thyroid to return to normal function. It is characterized by the disappearance of nervousness, irritability, poor appetite and depression. The color improves and the patient assumes a more cheerful attitude. This change is so noticeable that, when it does occur, it reminds one of the crisis in pneumonia. The rate of appearance of the three stages varies considerably with different patients. Sometimes the ankylosing stage is reached in a few months, while in other cases it requires several years.

The sequence of lowered B M R, abnormal Azorubin S appearance time, and alteration of the serum albumin-globulin ratio although not always occurring in this order, appear to be additional progressive effects of the infection in rheumatoid arthritis and must be corrected to obtain best therapeutic results.

In rheumatoid arthritis it is difficult to influence a low B M R. On the other hand, in a large number of patients with mixed and osteo-arthritis, the B M R can be increased with thyroid extract. Its value in these cases is as an adjunct to other forms of treatment and it should never be considered as an adequate remedy by itself. Successful thyroid medication is characterized by reduced nervousness, fatigue and depression, improved appetite and sleep, and by other signs of constitutional improvement.

CONCLUSIONS

1 The basal metabolic rate was within normal limits in 59 per cent, below normal in 24.3 per cent, and above normal in 16.7 per cent of 400 patients with chronic arthritis.

2 The number of cases showing basal metabolic rates below normal was essentially similar in the rheumatoid, the mixed arthritic and osteo-arthritic cases. However, in the rheumatoid group more cases showed rates above normal than in the other two groups.

3 In patients with mixed and rheumatoid arthritis, the basal metabolic rate varied with the activity of the disease.

4 The duration of the disease was greater in those patients with a basal metabolic rate above normal than in those with normal or sub-normal rates.

5 Small doses of thyroid extract, although not curative per se, frequently produced some improvement in joint symptoms and raised the general resistance

6 Thyroid extract is more effective in the mixed form of arthritis and in osteo-arthritis than in rheumatoid arthritis

The authors wish to thank George H Chapman for his advice and help in the preparation of the manuscript

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PLASMAPHERESIS EXPERIMENTS UPON THE INFLUENCE OF COLLOID OSMOTIC PRESSURE, WATER AND SALT IN EDEMA FORMATION

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NUMEROUS investigators have produced edema by a reduction of the plasma proteins. The reduction of the plasma proteins by repeated bleedings is called plasmapheresis. Leiter^{1,2} and Barker and Kirk³ were the first to carry on this work. Since that time numerous investigators, chiefly Shelburne and Egloff,⁴ Lepore,⁵ Darrow, Hopper and Carey,⁶ Weech, Snelling and Goettsch,⁷ Kylin⁸ and ourselves^{9,10} have carried on these experiments. Our method of plasmapheresis has been essentially the following. Five to eight hundred cubic centimeters of normal blood were obtained from the right or left ventricle of a normal dog. This blood was citrated, centrifuged, the plasma thrown away and the cells, after having been washed several times with Ringer's solution, were suspended in Ringer's solution in an amount sufficient to bring them to the original volume. The dog whose proteins were to be lowered was then placed on the table, a right heart puncture was done, and 500 to 800 c c of blood were removed depending upon the size of the dog. The cells of the first dog suspended in the Ringer's solution were then injected into the jugular vein of the second dog. The blood removed from the second dog was then centrifuged and the cells washed and suspended in Ringer's solution up to the original volume for the purpose of future reinjection. Reinjection of red cells in plasmapheresis experiments is necessary in order that anoxemia be excluded as a factor in edema formation. This process was repeated several times a day, depending upon the type of experiment. The dogs were allowed to drink as much water as they desired during the course of the experiment and were given previously determined amounts of either saline or water by stomach tube at each bleeding. A record was kept of the weight of the dog, the amount of blood removed, the amount of fluid intake, the amount of fluid output, the plasma protein level, the osmotic pressure of the plasma colloids, and the amount of edema. When we first undertook plasmapheresis for the purpose of developing edema in dogs, we decided to give only water by mouth, using no saline. Both Leiter, and Barker and Kirk, gave large daily amounts of saline to their dogs during the time they were attempting to produce edema. We thought that such large amounts of salt would have some effect on the amount of edema produced because correspondingly large doses of salt given to

* Received for publication March 29, 1937

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a nephrotic patient would be sufficient to bring on massive edema. Therefore in our first experiments we gave the dogs only water. We carried on several experiments under these conditions and were disappointed to find that we could not produce a marked edema. Despite the fact that we reduced the blood proteins to levels far below those at which Leiter, and Barker and Kirk obtained edema and despite the fact that the osmotic pressure of the plasma colloids was far below that of the usual nephrotic patient with edema, only a tendency to edema was produced. Slight edema would be formed quite readily whenever some other factor such as the application of straps about the legs or injury to a vein through frequent puncture produced an increase in venous pressure. In one such experiment (table 1) which lasted over a period of 13 days, the dog was given 14,500 c c of water and put out 13,730 c c of urine. The colloid osmotic pressure was reduced to values of 5.6 to 6.9 mm Hg*. At autopsy the dog showed practically no edema. Having failed to obtain any considerable amounts of edema by this method, we decided to repeat the experiment, using saline instead of water. In one such experiment (table 2) which lasted over a period of five days, the dog was given 7425 c c of saline and urinated only 3820 c c. He developed marked ascites and anasarca. A comparison of the two tables shows that the colloid osmotic pressure was reduced to approximately the same level in both experiments. Yet in the experiment where saline was given instead of water, the dog developed massive edema.

These experiments, of course, lead us to certain definite conclusions, namely, that salt is necessary in the formation of edema and that without salt, even though the colloid osmotic pressure be reduced to very low levels, only little if any edema can result (unless other factors such as a rise in venous and capillary pressures develop at the same time). We then attempted to produce edema in a 24 hour period by repeated bleedings during the day. Table 3 gives the results of such an experiment. Five thousand six hundred cubic centimeters of blood were removed by repeated bleedings and replaced with red cells and Ringer's solution in a 24 hour period. The dog was given 4760 c c of fluid and put out 940 c c of urine. We also made an attempt to study the salt intake and output on this dog. It was found that he took in 30 gm of salt during this period and put out 9.25 gm in the urine. In other words, there was a retention of 5.5 grams of salt per liter of water. This dog had marked edema at death. There were 500 c c of ascitic fluid and the tissues of the neck and legs showed free fluid on section.

Having demonstrated that it was possible to produce edema by reduction of plasma proteins in a 24 hour experiment, we decided to attempt the following type of experiment (table 4). Instead of suspending the cells in Ringer's solution before reinjecting them, we suspended them in 6 per cent gum acacia solution. The experiment was carried out in exactly

* Normal for the dog is 18.6 mm Hg

TABLE I

Date	Wt of dog, lb	Blood removed c c	Fluid given c c	Urine output c c	Specific gravity	Albumin %	Globulin %	Fibrinogen %	Total Prot	Osmotic pressure in mm Hg	Edema
8/17/31	30	1000	900 H ₂ O	650	1 005	3 49	2 69	0 41	6 59	17 9	No edema
8/18/31		1050	650 H ₂ O	1325	1 009	3 05	1 37	29	4 71		
8/19/31		1075	1450 H ₂ O	1300	1 006	3 1	1 52	40	5 02		
8/20/31		1050	1150 H ₂ O	750	1 007	2 27	1 04	33	3 64		
8/21/31		775	1450 H ₂ O	1210	1 007	1 97	98	26	3 21	5 6	Slight edema in legs below ropes
8/22/31		1200	1700 H ₂ O	1725	1 010	2 08	1 28	39	3 75		Slightly more edema below ropes
8/23/31		500	1050 H ₂ O	1100	1 007	1 78	1 14	46	3 38		Slight edema
8/24/31		1000	1700 H ₂ O	1315		1 32	99	35	2 66		Slight edema
8/25/31		800	450 H ₂ O	540	1 011	1 03	88	30	2 21		Little edema in hind legs
			Dog Vomiting								
8/26/31		1000	800 H ₂ O	790	1 010	1 31	1 07	40	2 78		Slight edema on body and legs
8/27/31		1000	1500 H ₂ O	1025	1 010	93	95	22	2 10		Same
8/28/31		500	1700 H ₂ O	2000	1 009	1 34	80	34	2 48		Only small amounts of edema of legs and body
		Total	14500	13730							

Autopsy showed only slight edema on the legs and body No ascites

TABLE II

Date	Wt of dog, lb	Blood removed c c	Fluid given c c	Urine output c c	Specific gravity	Albumin %	Globulin %	Fibrinogen %	Total Prot %	Osmotic pressure in mm Hg	Edema
10/6/31	26.5	1500	1500 saline	1100	1.015	3.8	1.69	0.44	5.93	17.3	
10/7/31		1500	1650 saline	1500	1.020	2.0	1.05	44	3.49		
10/8/31		1500	1425 saline	350	1.032	1.49	70	44	2.63		Slight edema
10/9/31		1000	1550 saline	425	1.021	69	47	23	1.39	5.8	Abdomen distended with ascites
10/10/31	28.0	1000	1400 saline	450	1.045	2.29	1.12	46	3.87	9.0	Slight edema of the legs Pitting edema on legs and abdomen
		Total	7425	3820							

Autopsy showed ascites and marked pitting edema on the legs and abdomen

TABLE III

Date	Weight, lb	Blood exchanged	Fluid given	Fluid recovered	Specific gravity of urine	NaCl given	NaCl recovered in urine	Edema	Plasma proteins
2-15-33 7 30 a m	27.5	1600 cc	200 cc Ringer's intravenously 500 cc saline orally			1.68 4.5			
2-15-33 1 30 p m	28.5	1500 cc	200 cc Ringer's intravenously 500 cc saline orally			1.68 4.5			
2-15-33 7 30 p m	30	800 cc	200 cc Ringer's intravenously 500 cc saline orally	500 cc	1020	1.68 4.5	7.15 gm		At 7 30 p m Total protein 1.72%
2-16-33 12 30 a m	32	800 cc	200 cc Ringer's intravenously 500 cc saline orally 1000 cc H ₂ O taken	None		1.68 4.5			
2-16-33 8 30 a m	34	800 cc	100 cc Ringer's intravenously 100 cc 30% acacia intravenously 500 cc saline orally	440 cc	1012	.84 4.5	2.12	Present	At 8 30 a m Total protein 2.56%
2-16-36 4 30 p m Dog died		Totals	250 cc H ₂ O 4760 cc	940 cc		Total 30.06 gm	Total 9.27 gm	Marked	

Dog had 500 cc of ascites at death. Tissues showed free fluid in neck and legs on cutting into them.
Autopsy also showed 150 cc of bloody pericardial fluid.

TABLE IV

In this experiment, plasmapheresis was carried on as follows. The blood was centrifuged, the plasma discarded and the cells were made up to the original volume with 6 per cent gum acacia in Ringer's solution

Date	Weight	Blood exchanged	Fluid given c c	Fluid recovered c c	NaCl given gm	NaCl recovered in urine	Plasma proteins	Colloid osmotic pressure mm Hg	Edema
2-23-33 9 a m	19.5	700 c c	200 c c Ringer's intravenously 400 c c saline orally		1.68 gm 3.6 gm		After bleeding 0.97%		None
2-23-33 2 p m	21.5	700 c c	200 c c Ringer's intravenously 400 c c saline orally		1.68 gm 3.6 gm		Before bleeding 2.1%		None
2-23-33 7 p m		700 c c	200 c c Ringer's intravenously 400 c c saline orally		1.68 gm 3.6 gm		Before bleeding 1.12%		None
2-24-33 1 a m	21.0	700 c c	200 c c Ringer's intravenously 770 c c H ₂ O orally	2100	1.68 gm 3.6 gm		Before bleeding 0.97%	15 mm Hg	None
2-24-33	Dog died		120 c c H ₂ O	480		20.07			None at autopsy
		Totals	3290 c c	2590 c c	21.1 gm	20.07 gm			

9.3 gm of gum acacia were recovered in the urine
Autopsy showed no edema—no ascites—veins were markedly distended

TABLE V

In this dog no plasmapheresis was performed but he was given water and salt in the same amounts as were the dogs on which plasmapheresis was done

Date	Weight	Blood exchanged	Fluid given c c	Fluid recovered c c	NaCl given	NaCl recovered in urine	Edema
3-20-33 10 40 a m	17.5	None	400 c c saline orally		3.6 gm		None
3-20-33 1 p m	18.5	None	300 c c Ringer's intravenously 400 c c saline orally		2.52 gm 3.6 gm		None
3-20-33 5 30 p m		None	300 c c Ringer's intravenously 400 c c saline orally		2.52 gm 3.6 gm		None
3-20-33 Midnight		None	200 c c Ringer's intravenously 400 c c saline orally		1.68 gm 3.6 gm		None
3-21-33	16.5		Water intake 100 c c Total fluid 2500 c c	2400 Total output 2400 c c	Total NaCl 21.1 gm	Total NaCl in urine 19.9 gm	None

At the end of the experiment, there was no demonstrable edema

the same manner as the previous experiment except for the addition of gum acacia. The blood proteins were reduced to levels far lower than those necessary to produce edema in any of our other experiments. However, in this experiment the colloid osmotic pressure of the plasma was at nearly the normal level for dogs. Under these conditions the dog was given 21 gm of salt and excreted 20 gm of salt. At autopsy there was no edema, the tissues were dry, and there was no ascites. It then became necessary to ascertain how a normal dog without any plasmapheresis would handle the same amount of water and salt. Accordingly, the experiment shown in table 5 was undertaken. In 24 hours the dog was given 2500 cc of fluid, mostly saline and Ringer's, and put out 2400 cc of urine. He took in 21 gm of salt and excreted 20 gm of salt. No edema was formed.

These experiments prove conclusively that the maintenance of the colloid osmotic pressure at the normal level by some inert colloid (gum acacia) is

TABLE VI
Summary of Experiments on Plasmapheresis in the Production of Experimental Edema

Types of Experiments	Plasma proteins	Colloid osmotic pressure	Excess salt	Edema
Plasmapheresis Dog drinking only water	Reduced	Reduced	Absent	None
Plasmapheresis Dog drinking saline	Reduced	Reduced	Present	Marked
Plasmapheresis replacing plasma with 6% gum acacia Dog drinking saline	Reduced	Normal	Present	None
No plasmapheresis Dog drinking saline	Normal	Normal	Present	None

This table shows that two factors are necessary in the production of experimental edema, namely reduction of the colloid osmotic pressure and adequate salt intake.

sufficient to stop any tendency to edema formation. Even when the protein levels were reduced to values far below the level at which edema usually appears in such an experiment when no gum acacia is given, no edema developed. These experiments prove conclusively that the tendency to edema formation is a function of the colloid osmotic pressure of the plasma and would tend to show that one of the main functions of proteins in the plasma is the maintenance of a normal colloid osmotic pressure. Table 6 summarizes the experiments on plasmapheresis and shows the effect of various factors in edema formation.

CONCLUSIONS

1. Plasmapheresis experiments on a dog in which the colloid osmotic pressure of the plasma is reduced to levels equal to or below those which

cause edema in man will not lead to edema formation or salt retention as long as the dog is given only water and a very much restricted intake of salt

2 The same experiment leads to marked edema formation and salt retention when the dog is given normal saline instead of water

3 Twenty-four hour plasmapheresis experiments in which the proteins are reduced to a very low level within 24 hours result in marked edema within this short period of time if the dog is given saline to drink

4 Dogs in which plasmapheresis has reduced the protein level below the usual edema-forming level but in which the colloid osmotic pressure of the plasma has been maintained by an indifferent colloid, gum acacia, develop no edema or salt retention

5 Normal dogs given large amounts of saline by stomach tube retain no water or salt

6 Retention of salt is due to filtration of protein-free plasma as edema Normally functioning kidneys will not excrete salt if it is prerenally deviated as edema by ultrafiltration in the capillaries

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THE DOCTOR HIMSELF AS A THERAPEUTIC AGENT^{*}

By W R HOUSTON, F A C P, *Austin, Texas*

IN recent years there has been increasing talk about the broader aspects of medical service. Medical men themselves have been anxiously considering not merely the building stones of medicine, but the plan of the entire medical structure. A great foundation has recently asked us for a free expression of opinion concerning American medicine. We are asked how well is medicine fulfilling its function to society, how can the benefits of medical science be best distributed, how shall medicine best be meshed with the economic structure? And these questions have led to further questioning as to the values that we have for distribution. We have considered not only the question of whether the conduits for conveyance of medical service are open, but also the purity of the sources of supply. From all this free and even voluble outpouring of opinion, it has come to light that despite there being many expressions of opinion that are merely slogan-mongering, expressions with more than a tinge of trade-unionism in them, there is also emergent much well-considered thought, the thought of informed and able men.

In all this discussion there has constantly echoed one recurring phrase, a phrase which it is my purpose to consider here, a phrase that has sometimes been thought to have grown so threadbare that it has been designated as merely a "smoke-screen" to conceal some unavowed purpose, the phrase, "Personal relations between doctor and patient."

Those who have most used this phrase have not been the most liberal thinkers. It has been employed rather by men who heretofore had been disposed to regard medicine as a tight, fast-set science, men accustomed to emphasize the science, rather than the art, of medicine, men who had previously looked askance on discussions of human relationship as the vapors of undisciplined thought. But now, from an unexpected quarter of the horizon, succor appears. In their anxiety to withstand change in the economic relationships of medical practice, these same men speak urgently of dangers to the relationship between doctor and patient. This relationship, which has received so little consideration in our councils, which has rarely been discussed at our medical meetings, has now become a citadel of refuge, a chief bulwark against socialization.

A recognition of the importance of the relationships between doctor and patient, even though belated, is none the less good. This relationship is indeed an overwhelming handicap to any plan for standardizing and mechanizing medical care. There are many things in medical work that can be standardized, to which methods of shop efficiency can be applied. The ap-

* Read at the St. Louis meeting of the American College of Physicians, April 19, 1937

plication of medical science to the care of swine and cattle has been best accomplished by mass standardization. The methods of pathology, immunology, clinical research and diagnosis have been brilliantly illustrated in our dealing with the domestic animals. In my State of Texas far more money is spent by the State on its veterinary service than on its public health work for human creatures, some evidence that the State is conscious that mass action is efficient in dealing with veterinary problems.

What distinguishes veterinary medicine from human medicine is just this relationship between doctor and patient. It is a relationship that has a long history. In the early history of medicine, it comprised all that the doctor had to offer the patient. It is only very recently that medicine has had more to give. A survey of medical history acquaints us with many illustrious names. Step by step these men contributed to an understanding of anatomy, physiology and to the description of clinical syndromes, but if we except such courage and consolation as the physician might offer, they had very little to give by which the patient could profit. Historians sentimentalize the practical values of ancient medicine. One scans the pages of Hippocrates in vain for any treatments of specific value. The pages of medical history read like the log of an old-fashioned ocean voyage, in which it is noted that on such a day a whale spouted, on such a day a flying fish was sighted, or a bit of driftwood, but in which no mention is made of the huge prevailing fact that what was constantly seen day by day, almost to the exclusion of other sights, was the unending green waste of water. And this inevitable circumambient ocean is, by analogy, in medical history the "personal relationship between doctor and patient."

By this it is not meant to say that doctors didn't do things for their patients. They did a great deal. The need of human beings for action when in distress, some sort of action, without much question as to whether the act was wise or foolish, was met. Medicine, as the anthropologists tell us, was originally magic. Pharmacology is a late development. Medicines were prescribed that produced an overt effect,—vomiting, sweating, purging.

In a word, the medicines used were placebos, something to please the patient. The doctor, himself, by words of cheer and comfort sought to please the patient. His medicines were merely symbols to reinforce this purpose. Perhaps I may seem to be stretching the meaning of the word, placebo. It is ordinarily taken to mean a procedure undertaken to gratify the patient's desire for active intervention, but which is understood by the doctor to be inert and useless. For example, a bogus puncture. There is, however, a second sort of placebo, which seems to be no less a placebo, in the employment of which the patient's attitude is the same, but where the doctor's attitude differs in that though the procedure is valueless, the doctor esteems it to be valuable. For example, an ovarian tablet. As to the first type of placebo little need be said. It is a type of treatment not uncommonly used, effective at times yet not held in high esteem. The second sort of placebo the type which the doctor fancies to be an effective

medicament but which later investigation proves to have been all along merit, is the banner under which a large part of the past history of medicine may be enrolled. The herbs of the Indians, the pharmacopœias of the Orient, a large part of the contents of our older books on medicine are made up of these placebos in which doctors erroneously had faith. Their usefulness was in direct proportion to the faith that the doctor had and the faith that he was able to inspire in his patients. But related to this second group of placebos is a third group, a group in which the placebo used while it is believed in by the doctor, is no longer harmless but harmful, sometimes very dangerous. It would seem peculiarly contradictory to speak of the painful and dangerous placebo, yet men are so constituted that they feel the need in dire extremity of resorting to dead measures. Nervous patients, in particular, feel that a certain standing and sanction is bestowed on their maladies when violent therapeutic measures are used.

The great lesson, then, of medical history is that the placebo has always been the norm of medical practice, that it was only occasionally and at great intervals that anything really serviceable, such as the cure of scurvy by fresh fruits, was introduced into medical practice. By and large, the doctors were, as reported by that sane and shrewd observer, Montaigne, a danger to their patients. The medical historian is apt to mislead us when he speaks of the learned and skilful doctors of the past. While undoubtedly exceptional instances might be unearthed to show that these physicians accomplished something for the somatic good of their patients, in the large view we are forced to realize that their learning was a learning in how to deal with men. Their skill was a skill in dealing with the emotions of men. They themselves were the therapeutic agents by which cures were effected. Their therapeutic procedures, whether they were merit or whether they were dangerous, were placebos, symbols by which their patients' faith and their own was sustained.

The history of medicine is a history of the dynamic power of the relationship between doctor and patient. Through centuries when doctors were doing more harm than good this dynamic force has sustained the medical profession in the esteem of their clientele, it has inspired their fellow citizens with such faith in its values that they were willing to give economic support to the doctor. However little the doctor had to offer it was to him that men turned in the distress of illness. When we observe the honor and emolument bestowed on the physician throughout the ages we are forced to exclaim, "Oh rare cogency of the relation between doctor and patient."

The scene has changed. With the name of Pasteur we associate an increasingly rapid acceleration in our emancipation from the sway of the placebo. The prestige of medicine has constantly mounted higher and higher and this prestige rests on a solid foundation. So rapid have been the acquisitions in bacteriology, immunology, in sanitation, so increasingly efficient have we become in hygiene, in dietetics, in surgery, in the executive distribution of the scientific plans through departments of health and organizations for nursing, so great has been the eagerness to acquire new knowledge

and to institute fresh researches, that we have been tempted to forget our origins, the long historical past of "personal relations between doctor and patient" Not that there are not enough reminders of it The relation between nostrum-vendors and their patients, between chiropractor and patient, between quack of whatever stripe and patient should suffice to remind us of our past The fact that States and legislatures have shown themselves so kindly disposed towards the charlatan and his placebos gives one to see how strongly entrenched in the popular mind is the precedence of the healer-patient relationship over the claims of somatic medicine No one considers applying the principles of osteopathy to pigs and steers, because osteopathy is a human relationship, a "personal relation between doctor and patient" It is not through cults that exploit personal relationship but through our knowledge of bacteriology, immunology and dietetics as embodied in veterinary science that the legislature is expecting to see swine and cattle brought sound and healthy to the slaughter pen

What is the something more, something different from the veterinary medicine that the patient expects when he goes to the doctor? It is certain that were he subjected to Socratic questioning no very clear answers could be had The patient is aware of the doctor's prestige but he is unaware of what sort of foundation it rests on Between what he expected as magic potion or compelling ritual from the doctor-priest and what he expects from scientific medicine there lies a bond of kinship For many a patient the drug prescription is still heavily tinctured with magic, for him the doctor is a medicine man, a drug-giver, and it may be regarded as an ameliorating circumstance that when such a patient strays off after a drugless cult in addition to being in revolt against common sense, he is also in revolt against outworn superstition

But what the patient most imperatively demands from the doctor is, as it always was, action However the doctor may spar for time by delays of diagnostic study, these delays only whet the patient's appetite for decisive action In a large and constantly growing number of instances the physician is able quite satisfactorily to render the service expected of him When it is a question of diabetes or myxedema, anebiasis or syphilis, beriberi or macrocytic anemia, the physician sets about his work with resolute confidence In the group of diseases for which nursing care is our chief resort, bronchial pneumonia, typhoid fever, and the rest, the line of procedure is scarcely less well-defined In situations of utterly hopeless outcome the physician at least understands that consolation and the relief of suffering is his rôle

But what of the patients who fall into none of these classes? What proportion are they of all those that seek treatment? Sydenham estimated that they comprised a sixth of all his patients Charles Emerson, in his recent book, estimates them as half, and estimates further that half the symptomatology of the somatically ill is nervous These patients are even more demanding than the somatically ill for action As a class they are

little inclined to listen to sincer reasoned counsel, however adroitly it may be worded. They are usually disposed to question the diagnosis if told they have no somatic disease. The approval of these patients is essential to the doctor's success in practice. What can he do? What he very often does is to treat them with placebos, coupling the placebo with such suggestions for improved mental hygiene, and better ways of living as he can sandwich in. If reproached for degrading the pharmacopeia to the rôle of placebo, these men retort, "Well, after all, a man has to be practical."

Often enough, doctors of little critical discrimination come to believe in the placebo just as their faith is able to impart to the patient the faith that heals, and the faith seems to be justified by its fruits. Such men argue hotly for their placebos, since it is a well-known trait of character that ire is engendered by matters of faith, not by matters of demonstration, men fight for a belief, not for a statistical deduction. These are they that loudly affirm "thou shalt have no other placebos before mine," and pursue with bitterness the alien placebo-mongers of another cult.

When thoughtfully considered, this situation is not one to be regarded with comfort. Medical men are not without misgivings about the spurious psychotherapy that they are under constant temptation to practice. Yet the path to development of a better psychotherapy is full of obstacles. The doctor's training in the laboratory and the ward has offered few opportunities for the development of any aptitude in dealing with the problems of personality. Doctors consider that their vocation is to deal with things that can be weighed and measured and that the reactions of the cerebral cortex and the autonomic nervous system are too intangible for them to deal with. As a distinguished member of this body, and contributor to this program recently wrote me

"I suppose that I am particularly bitter about the people whom we may as well call neurotics, who, as you say, take up so much of an internist's time. They are the people who drove me out of practice. I never could see any sense in paying any attention to them because, as your word picture of them so graphically shows, they have neither sense, nor gratitude, nor any idea of cooperation, nor any qualities that might endear them to man, woman or child.

"I cannot understand why those of us who have trained ourselves to take care of people who have organic disease can't be allowed to take care of organic disease. Why won't these people take our word for it that there is nothing the matter with them and let it go at that? I suppose I have as many somatic sensations as anybody on earth but I explain them to myself in a physiological way. Why can't an intelligent neurotic take the same sort of advice that I give myself? There seems to be no way of handling them except that sort of semi-quackery that some highly respectable members of our fraternity are able to get away with so successfully."

Here is a credo. There is a confession of faith. It has led a highly successful internist to give up his practice so he says, and seek other employ-

ment It is as though one said "I don't like feces," and refused to treat dysentery or cholera The brain and nervous system are organs of the body, their functioning is observed in behavior and feeling Now, when it has become a pride of medical research that we study function, when studies of the function of the heart, the kidneys, the liver, are constantly multiplied, why refuse to consider the functions of the master tissues,—the brain and vegetative nervous system? Wouldn't it be about like refusing to consider disorders of the circulation though admitting a willingness to treat another system of the body?

And yet the above statement is one of the most logical statements that could be made It is as logical as the rack and the faggot for the heretic What could be more logical—when eternal torture in hell awaits the heretic—how humane to torture him now in order to spare him endless torture The flaw in the logic is that there is no hell of eternal torture, the flaw in the logic of my correspondent is that behavior and feeling do not subsist in some separate ghostly realm but form a part of the organic activities of man The postulate that underlies my correspondent's viewpoint is physiologically untenable

And another thing—a rather base practical point to which I would like to invite you—is that my correspondent's view won't pay out Not to refer to the fact that it has driven him from the practice of medicine (he is spoofing about that), a much worse thing is it will tend to drive patients away and drive many doctors to penury In Germany this viewpoint has long existed It was expressed by the Chancellor of Washington University today when he said, "The doctor had better stick to his last" The result of this credo in Germany has been that the offices of doctors are empty while those of naturopaths overflow, that quacks abound as nowhere else, that finally the Hitler Government has set up the quack as the State Medicine The Fuhrer in medicine is a Naturopath

An even greater obstacle, however, lies in the patient himself The patient's philosophy is usually the traditional one that the mind and body are quite distinct affairs, that he has come to see the doctor about his body, and that if the doctor begins to talk about psychic matters he is being cheated There was a certain admirable unity in primitive days when the doctor-priest offered the magic potion to exorcise the demon of sickness That unity has been lost We now face a hopeless dichotomy It will be an uphill road to try to explain to the patient the unity of the organism, that mind is an aspect under which the integrated body is to be regarded, that the soul represents the interplay between the organism and its external and internal environment Any such talk the patient would regard as an evasion, as making light of his trouble, and the physician who expounds such views may find that his patient will seek another who is more in accord with his own viewpoint, and, as he will doubtless believe, possessed of a keener apprehension of the diagnostic problem

But it is time to turn from the question of difficulties and consider

the search for a possible solution to this question of how to deal with the 75 per cent of nervous symptoms which present themselves in our patients, to consider dealing with them in some more thorough-going way than through the employment of tonics and sedatives, to seek whether there may not be something more admirable than the resort to placebos. In the first place it may be asked, can nervous symptoms be studied and dealt with by the methods of the exact sciences.

I have recently read a little book, "Einfluss der Gemutsbewegungen auf den Körper." In this account of the influence of emotional disturbances on the body, I find some 16 pages of bibliography devoted chiefly to a record of experiments, most of which attempt to weigh and measure those things that we are wont to call intangible. There are innumerable experiments recording the effect of emotion, not only on heart rate and blood pressure but on the size of the heart, not only on the titer of acidity of the gastric juice and on gastric motility but on the position of the stomach, not only on the frequency and amount of urinary output but on the chemical composition of the urine, experiments that indicate the effect of emotion on blood chemistry, on electrical reactions in the skin. Much of this subject matter was finely developed in Dr Cannon's oration last year. These studies go far to show that what we have called intangible is really tangible. Emotional life does, it is true, admit of exact scientific study. From a consideration of these experiments we will indeed get many fruitful conceptions of great help in practical daily work. Physiological laboratories, however, deal as a rule with brief and elemental emotions. They have not yet arrived at the point where they can take account of these neuro-muscular dispositions that are concerned in hope and courage, in depression and loss of confidence, in the long rankling of envy or the serenity of peaceful acquiescence. Suggestive as are these studies, they do not put into our hands diagnostic instruments for the study of our nervous patients. Nor do they tell us in any unequivocal way what we must do for them.

Another solution that has in recent times been much emphasized is that the practitioner of medicine should acquire the psychiatric viewpoint. There must be a closer liaison between psychiatry and medicine. There can be no doubt that internal medicine not infrequently is biased toward an explanation of symptoms as necessarily due to structural and chemical change when the true explanation lies in a disturbance of the emotional life. Nothing would seem more logical than that the psychiatrist, through his familiarity with the gross disturbances of reaction and behavior, should bring us help in dealing with milder disturbances. As the late Dr Salmon pointed out, we cannot refuse to the study of the neuroses our active concern for the very good reason that we have accepted from the state the responsibility for the care and direction of the insane. If we accept the responsibility for the care of advanced sickness of the soul, we must all the more be attentive to an incipient sickness.

There can be no doubt that there does exist a chasm between psychiatry

and medicine. A circumstance that tends to widen the chasm is the profound reluctance of the nervous patient to be placed in the category of psychiatric patients. He insists, "I am not crazy," and resents even the suggestion that he may have symptoms that are not of somatic origin. It might be an excellent thing if all nervous patients could be cared for by skilled psychiatrists, but in many instances the very crux of the difficulty is that the patient does not consider himself a nervous patient. The battle in many cases would be nearly won if the patient could be induced to place himself in the hands of a psychiatrist, but actually the heat of the battle is over before the malady encounters its proper antagonist.

It is indeed true that the psychiatrists have contributed much to our understanding of the nervous patient, but the practitioner is likely to feel that the psychiatrist he knows is chiefly concerned with the problems of custodial care and has small opportunity to become conversant with such organic nuances, such emotional problems as are daily encountered in practice. He scarcely understands that by the psychiatric outlook is meant a consideration of the broad issues of the dynamics of personality.

If the practicing physician turns to the school psychologists for aid, his findings may prove to be even more barren. Non-medical psychologists are at a considerable disadvantage in that they do not give sufficient weight to the problems of sleep and diet, the systole and diastole of effort and repose.

One cannot advance against the disorders in the emotional sphere by mere reasoning. By the emotional sphere is meant not merely fear, rage and sex-love, but the whole inner reaction-mechanism, the reactions of single organs, of functional systems, the reactions of mood, of desire, of the inclinations and vital drives of the integrated organism. It is these great vital tendencies that the psychobiologist conceives as furnishing the motive power. Their chief seat is the thalamus, the basal ganglia, their expression is through the autonomic nervous system. The intellect, the cortex is their servant, its mission to find means for their satisfaction. If the mind is the steering wheel, the emotional life is the motor, or a better analogy, the vital tendencies dictate the direction and the goal while the mind finds the path that leads thither. It is well to seek new analogies to reinforce the truth that reason is servant, that vital tendencies as expressed in the emotional life are master.

As the patient faces the doctor he believes in certain things about himself which the doctor doesn't believe. The patient has faith in his malady which the doctor doesn't share. Faith is belief. It is a belief in which the thalamus has a stronger share than the cortex. The doctor's reasonable hope for cure rests on making such environmental changes as will alter the emotional status of his patient. The environmental factor of most moment is likely to be the physician himself. He will prevail if his faith is stronger than the patient's faith. Icy reasoning will not suffice. A strong enough faith, even in his placebos, may be enough, but as knowledge advances faith

in placebos declines The faith needs a firm foundation How shall such a foundation be laid?

A great deal is said about changes to be made in the patient's outlook and viewpoint. Not much about what the emotional attitude of the doctor shall be. Faith is an emotional attitude of warm confidence toward a situation. Freud, in discussing the "personal relationship of patient to doctor" asserts that for success in the relationship the patient must love the doctor, the so-called transference. This contribution to scientific exposition of the doctor-patient relationship is nothing to startle us. He doesn't say that the doctor must love the patient. Yet the doctor's attitude toward the patient is perhaps more fundamental than the patient's attitude toward the doctor. John Dewey, in his book, "A Common Faith," has shown that the faith to which all wise men, of whatever race or creed, may subscribe is a humanistic faith, and may be expressed as a sublimation and reinforcement of those human relationships that are cherished by every man. He must be a father filled with wise benevolence, a brother with consciousness that he shares in embryo all the weaknesses and frailties of the patient, a friend that knows the art of showing himself friendly.

Every man knows that emotional attitudes are more readily communicated than ideas. A dog or a child can understand an emotional attitude. The simplest souls can grasp the thalamic component of belief. The subtlest mind also yields to the persuasive drive of emotion, to the affective situation in which he finds himself. The dweller in the Orient unconsciously acquires enough of the spirit of acquiescence and inner calm to gain the low arterial tension of Oriental neighbors. The faith that heals, heals not through argument but by contagion. But to heal, faith must have substance. A speculative balance of probability is not enough. The faith that heals must have deep roots in the personality of the healer. A recent best seller in the realm of popular psychology, "The Return to Religion," written by a well-known psychologist, suggests as a cure for the feebleness of the doctor in the doctor-patient relationship that he return to the rites and formulas of the church. It is true that these express in fit and beautiful words many truths that seem to fade and perish when put into the clumsy terms of science.

But this suggestion won't help us. The faith about which reservations are kept has no living force. The faith that will avail the doctor must be grounded in his own psychobiologic conceptions. One of the most hopeful moves in medical education is teaching to first-year students the elements of psychobiology. A system of belief is implanted best in the young. It would be my suggestion that psychobiology be taught in the premedical years, that the doctor-patient relationship be the beginning of medical study. A deep insight into this fundamental philosophy is a chief concern of the internist.

I know no short definition of the word "internist," but I conceive of him that he is a type of general practitioner who, having delegated to workers in special fields a large number of his cares, has a special opportunity to gain

a vantage-point from which he can get a larger survey of the field of medicine. From this vantage-point he can see what problems press most instantly for solution. He it is who most correctly can select the point where therapeutic emphasis should fall, can judicially assay the worth of the rival claimants for priority in dealing with the sick man's problem.

To him then we would best address the question, "How can the 'personal relationship between doctor and patient' be made more fruitful for good? How can the doctor himself, as a therapeutic agent, be refined and polished to make of him a more potent agent?"

"What shall be the foundation of his faith? Is he to employ the placebos that he scorns when employed by the uncultured, or is he to find a way to educate his public to demand something different, something far better of him?" I leave this discussion in the form of a question, but a very pertinent and pressing question. A right answer will lead to the physician's occupying a position of even greater dignity in the social order than the high place he now holds.

ABSCESS OF MEDIASTINUM FOLLOWING ACUTE TONSILLITIS^{*}

By CHESTER S. KEEFER, M.D., F.A.C.P., Boston, Massachusetts

AN abscess of the mediastinum is a rare complication of hemolytic streptococcal infection of the throat. Recently such a case was observed and, following surgical treatment, the patient recovered completely. A summary of the case follows.

CASE REPORT

Following an acute tonsillitis and pharyngitis, a man develops painful and difficult swallowing, pain between the shoulder blades, fever, and leukocytosis. Examination showed signs of a mass in the posterior mediastinum. Abscess containing hemolytic streptococci drained. Recovery.

A man, 46 years of age, was admitted to the Boston City Hospital on account of fever and sore throat. Five weeks previously he had an attack of coryza and tonsillitis but it was not severe enough to confine him to bed. He continued with his daily work for two weeks, when he was forced to remain at home on account of chills, fever, and difficult and painful swallowing. This was accompanied by attacks of coughing which were productive of mucopurulent sputum. During the third week of his illness the chills and fever continued and the pain and difficulty in swallowing increased. In addition, he had some pain and discomfort about the base of the neck which radiated into the occiput during swallowing. The temperature gradually became lower and he felt somewhat improved insofar as his sore throat was concerned, but the dysphagia continued.

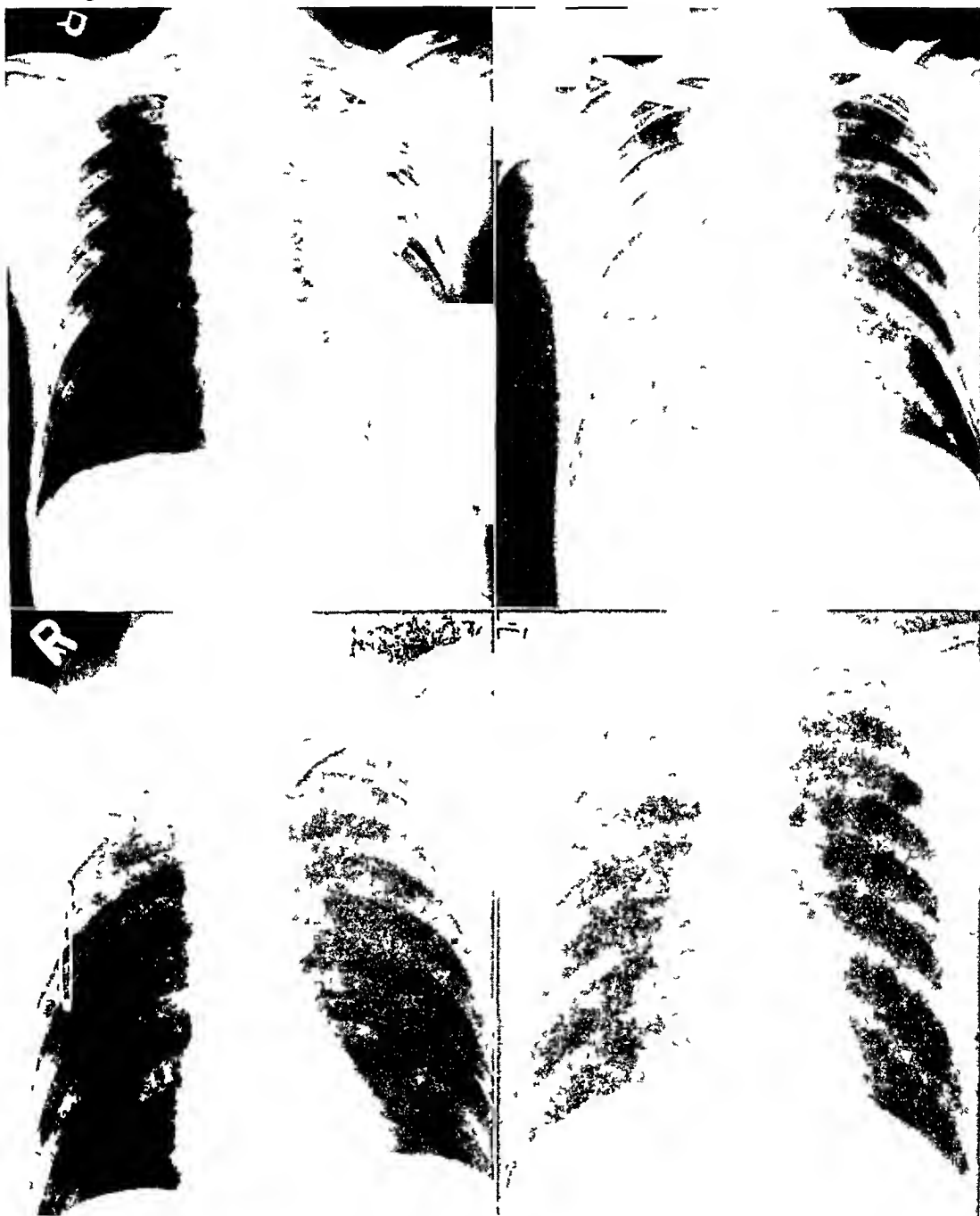
The physical examination showed a man who was acutely ill and pale. He had very few complaints but it was difficult for him to swallow liquids or solid foods. The temperature was 101.5° F. The throat was red and the pharynx seemed edematous and swollen. Palpation of the pharynx failed to reveal any localized mass although the mucous membrane was swollen. The lymph nodes of the neck were not enlarged, and the thyroid was not palpable. The trachea was in the midline and it could be moved lateralward without discomfort, it moved up and down on swallowing but this caused some discomfort. There was no swelling of the neck and no areas of tenderness on deep pressure. The movements of the cervical spine did not seem limited in extent. The examination of the chest failed to show any abnormal areas of prominence and the superficial veins of the chest wall and the jugular veins were not swollen. There was no retromanubrial dullness, no displacement of the heart or mediastinum laterally. The lungs were clear throughout. The heart was in normal position and the sounds were clear. Over the upper dorsal spine there was dullness extending from the first to the fourth dorsal spine, and over this area the whispered voice and breath sounds were distinct and bronchial in character, but aside from these abnormalities there was nothing distinctly abnormal to be made out on physical examination of the chest.

^{*} Received for publication July 27, 1937.

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4

FIG 1 Roentgen-rays of chest in patient with abscess of mediastinum (1) Roentgen-ray on first day of admission (2) Roentgen-ray on fourth day of hospital visit—note the enlarging mediastinal shadow (3) Roentgen-ray of chest 4 days after operation (4) Roentgen-ray of chest 2 months after operation

The abdomen was soft and no organs were palpable. The extremities, genitalia, and reflexes were normal.

Laboratory examinations showed 3,860,000 red blood cells per cubic millimeter and hemoglobin of 74 per cent (Sahli). The total white blood cell count was 25,000 per cubic millimeter with 85 per cent polymorphonuclear cells. The urine was clear and normal.

The roentgen-ray examination showed the heart in normal position, the lung fields clear. In the superior mediastinum there was a bilateral rounded shadow with concave borders, slightly more prominent on the right side than the left. It was distinctly supra-aortic, and it had not displaced the trachea laterally nor the aortic arch downward (figure 1).

Fluoroscopic examination showed that this shadow was retro-esophageal and in the posterior mediastinum. The esophagus was displaced anteriorly and slightly to the left. As the barium entered the esophagus, it paused momentarily at this area before passing downward.

In summary, then, a man had an acute tonsillitis and pharyngitis which was followed by difficult and painful swallowing, fever, and leukocytosis. Examination of the chest showed decreased resonance and increased whispered voice sounds over the upper dorsal spine, a bilateral rounded shadow in the superior mediastinum by roentgen-ray, and anterior displacement of the esophagus by fluoroscopy. From the clinical course of the illness, together with the above findings it seemed highly likely that the process was an abscess in the posterior mediastinum. This clinical diagnosis was supported by surgical operation.

Course of Illness. The course of the temperature is shown in figure 3. On the seventh day of his hospital admission Dr. I. J. Walker operated by entering the posterior mediastinum, resecting a portion of the second, third, and fourth ribs close to their articulation with the spine, and opened an abscess containing 300 c.c. of thin purulent material. The pleura was not entered and a drain was inserted. Following the operation there was an increase in the temperature for several days, but it gradually subsided and returned to a normal level within 14 days. The pus from the abscess contained a pure culture of hemolytic streptococci and the drainage was profuse for several weeks. Due to the anemia, he received two blood transfusions and improved considerably. After several months the cavity gradually diminished so that very little drainage was evident. He gained weight and felt greatly improved. When he was seen two months after the operation, he appeared well, had returned to work, and there was only a small draining sinus in the back.

COMMENT

The subject of abscess of the mediastinum has been discussed most thoroughly in the classical monograph of Hare¹ on mediastinal diseases. More recent essays on the subject are those of Neuhof,² Fischer,³ Lerche,⁴ Lambert and Berry,⁶ Heuer,⁷ Graham, Singer and Ballou,⁸ Farnum,⁹ and Malnekoff.¹⁰

In the present case, it seems likely that the infection of the posterior mediastinum resulted from an extension of the infective process in the pharynx to the retrovisceral space. The anatomical relations are illustrated in figure 2, which is reproduced from Lerche's⁴ paper. It is seen that the retrovisceral space extends directly from the pharynx at the base of the skull to the posterior mediastinum. The other possibility, of course, is that the abscess arose from suppurating lymph nodes in the posterior mediastinum.

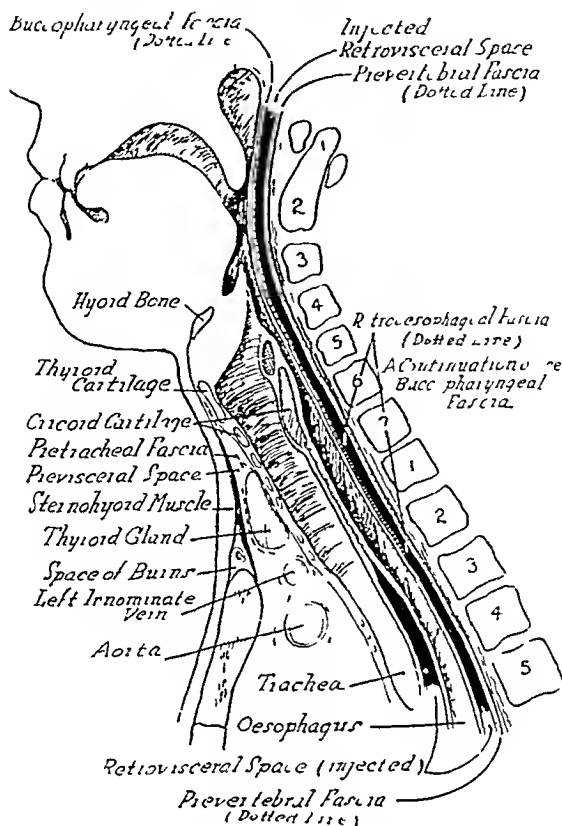
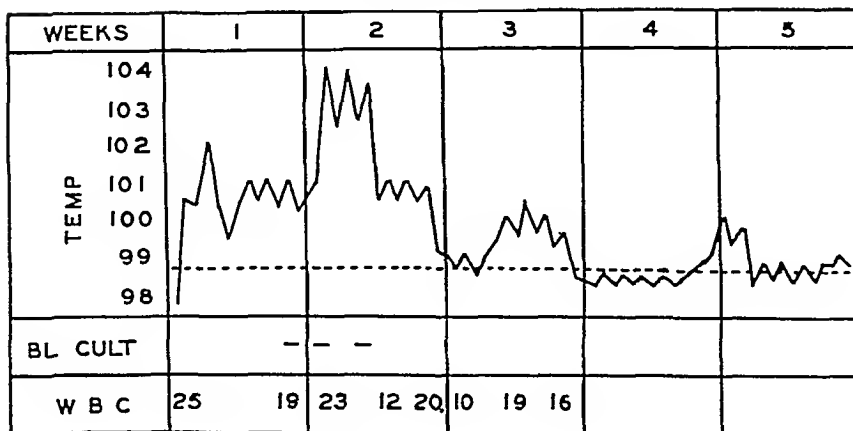


FIG 2 Diagram showing injected retrovisceral space (Reproduced by permission of Dr William Lerche, Arch Surg, 1924, viii, 247)

H S — MEDIASTITIS



↑
OPERATION

FIG 3 Temperature chart of patient with hemolytic streptococcal abscess of mediastinum
White blood cell count is recorded in thousands

This type of infection has been studied extensively by Leiche⁵ who emphasizes the importance of mediastinal lymph node infections in the causation of mediastinitis. It is analogous to the retropharyngeal lymph node infections with abscess formation in children, the main difference being in the location of the infection.

In general, acute mediastinitis is uncommon but, inasmuch as a small number of these cases are of such a nature that they can be treated surgically, it is of importance that they be recognized. For purposes of discussion, it is convenient to divide these cases into two main groups: (1) the diffuse phlegmonous variety and (2) localized abscesses of the mediastinum. Inasmuch as the diffuse phlegmonous variety may be only a part of a more widespread infection and therefore not amenable to treatment it can be dismissed from the present discussion.

Localized abscesses in the mediastinum can be divided, according to the situation of the suppurative process, into abscesses in the anterior or posterior mediastinum. This division is of considerable significance insofar as treatment is concerned.

Abscess of the Anterior Mediastinum An abscess in the anterior mediastinum results from (1) an extension of an infection from the neck, such as erysipelas, or infection following surgical operations, (2) an osteomyelitis of the sternum, (3) suppuration of lymph nodes, (4) an extension of an infection from the lung to the mediastinum. An abscess in this location tends to extend to the exterior and may present in the suprasternal notch or at the anterior border of the sternomastoid muscle. It may gravitate downward and cause a painful, tender area in the region of the xiphoid. Rarely such abscesses may point beneath the sternoclavicular region or perforate into the interspaces in the parasternal line.

Abscess of the Posterior Mediastinum An abscess in the posterior mediastinum results from an extension of an infection from the retropharyngeal space or from the esophagus. Other causes are extension of an infection from the spine, abdomen, lung, or pleural cavity. These abscesses show only a slight tendency to approach the surface and they commonly extend upwards or downwards in the mediastinum. They may rupture into the pleural cavity, the trachea, bronchi, esophagus, or pericardium. Indeed, when they are unrecognized or neglected they may even point in the posterior triangle of the neck or extend to the retroperitoneal space and appear in the groin.

Symptoms and Signs Referable to the Chest or Extension of the Infection to a Neighboring Organ In the main, symptoms arising from pressure of various anatomical structures of the mediastinum are less conspicuous with an abscess than with a neoplasm, and at the onset the symptoms of infection predominate, it is only later that the symptoms and signs of compression occur.

Pain beneath the sternum and radiating into the back, or pain between

the shoulder blades or referred along the intercostal nerves on one side are common features

The irritative phenomena consist of cough, dyspnea, painful and/or difficult swallowing, and painful movement of the trachea, or paroxysmal hypertension. Dysphagia is present when the process is situated in the posterior mediastinum and wheezing respiration occurs when there is compression of the trachea or bronchi, on rare occasions the bronchi may be compressed to such an extent that atelectasis occurs.

On occasions, the development of a mediastinal abscess is so insidious that it may be obscured by the symptoms and signs resulting from the extension of the process to a neighboring organ. The various paths of extension of an infection from the neck or mediastinum have been studied extensively by Lambert and Berly,⁶ Fuirstenberg and Yglesias¹¹ and Collier and Yglesias.¹² It is well to be familiar with the various possibilities, since foci of infection may appear in various areas and have their origin in the mediastinum. Thus, one may find extrapleural abscesses, empyema, abscesses in the neck, or perforation of the trachea, bronchus, esophagus, or lung. More rarely the infection extends to the pericardium, the peritoneum or the retroperitoneum. Infections in these areas, then, should call one's attention to the mediastinum as a possible focus of infection.

Roentgen-Ray Examination of the Chest The roentgen-ray of the chest will show unilateral or bilateral triangular shadows with the apex pointing caudad and superimposed on the heart shadow, or there are rounded or triangular shadows in the superior mediastinum. There may be an associated empyema or extra-pleural abscess which obscures the lung fields. In the case of abscesses in the posterior mediastinum, the esophagus is often displaced anteriorly and to either side of the midline. All of these signs should be looked for and, when they are present, the diagnosis of mediastinal abscess should be entertained. The examination of the patient under the fluoroscope should include both an anterior-posterior view as well as a lateral one. The roentgen-ray diagnosis has been discussed recently by Kornblum and Osborn.¹³

Diagnosis of Mediastinal Abscess The diagnosis of an abscess of the mediastinum depends upon the following features:

- 1 A history or the presence of a condition which is capable of causing a mediastinal infection
- 2 The constitutional symptoms and signs of an infection
- 3 The localizing symptoms and physical signs in the mediastinum due to involvement of various anatomical structures
- 4 Signs resulting from an extension of the process to neighboring organs
- 5 Characteristic roentgen-ray findings in the chest
- 6 Finding an abscess on exploration

When the above features are present one is justified in making a diagnosis of acute mediastinal abscess.

Treatment The diagnosis should be made as early as possible, inasmuch as the only possibility of recovery is surgical drainage of the abscess. There are, of course, the exceptions in which the abscess is drained by rupture into a bronchus⁹ or the esophagus, or by aspiration¹⁰. These instances occasionally occur when the abscess is overlooked and, while recovery may follow such a rupture, it is more common for death to follow such an accident.

In the present case, the posterior approach was used with success. Other methods which are recommended are drainage of the abscess through an incision in the neck with a drainage tube inserted into the mediastinum from this point.

SUMMARY AND CONCLUSIONS

A case of abscess of the posterior mediastinum following tonsillitis due to hemolytic streptococcus infection is recorded. Complete recovery followed surgical drainage of the posterior mediastinum. The clinical features and the course of these abscesses are summarized.

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CORONARY ARTERY DISEASE, A HISTORICAL SKETCH¹

By FRANK T FULTON, *Providence, Rhode Island*

INTEREST in any subject is usually accentuated by some study of its early history, and in connection with some of the now well understood diseases a fascinating story may be written

Medical students of 20 years ago seldom, if ever, heard of the clinical diagnosis of coronary thrombosis Angina pectoris on the other hand was frequently discussed, that diagnosis, when made, carried with it in the minds of most, the sentence of a short life, terminating in sudden death Now-a-days coronary thrombosis is up for daily discussion in a routine hospital visit, a fairly good guess can be made as to what artery is out of function and to the surprise of many, more than half of the patients go on to a satisfactory recovery

This short sketch will make no attempt to cover clinical or pathological detail but will deal with incidents and men and their places in the development of our knowledge of coronary artery disease The story, in this instance, as everyone knows, really began with William Heberden, whose first observations were made public in 1768 These were reported at a meeting of the Royal College of Physicians in London Even at the risk of tedious repetition, some of his description will be quoted He had just been referring to the various types of chest pain, vague, inconsequential and otherwise Then he said

But there is a disorder of the breast marked with strong and peculiar symptoms and not extremely rare, which deserves to be mentioned more at length The seat of it, and sense of strangling, and anxiety with which it is attended, may make it not improperly be called angina pectoris

They who are afflicted with it, are seized while they are walking (more especially if it be up hill, and soon after eating), with a painful and most disagreeable sensation in the breast, which seems as if it would extinguish life, if it were to increase or continue, but the moment they stand still, all this uneasiness vanishes

In all other respects, the patients are, at the beginning of this disorder, perfectly well, and in particular have no shortness of breath, from which it is totally different The pain is sometimes situated in the upper part, sometimes in the middle sometimes at the bottom of the *os sterni*, and often more inclined to the left than to the right side It likewise very frequently extends from the breast to the middle of the left arm The pulse is, at least sometimes, not disturbed by this pain, as I have had opportunities of observing by feeling the pulse during the paroxysm Males are most liable to that disease, especially such as have passed their fiftieth year

After it has continued a year or more, it will not cease so instantaneously upon standing still, and it will come on not only when the persons are walking but when

* Received for publication August 14, 1937

they are lying down, especially if they lie on their left side, and oblige them to rise up out of their beds. In some inveterate cases it has been brought on by the motion of a horse, or a carriage, and even by swallowing, coughing, going to stool or speaking, or any disturbance of mind. In one or two persons, the pain has lasted some hours, or even days, but this has happened when the complaint has been of long standing, and thoroughly rooted in the constitution. Once only the very first attack continued the whole night.

I have seen nearly a hundred people under this disorder, of which number there have been three women, and one boy 12 years old. All the rest were men near, or past the fiftieth year of their age.

The termination of the angina pectoris is remarkable. For if no accident intervene, but the disease go on to its height, the patients all suddenly fall down, and perish almost immediately.

One hundred and forty-three years later, before the same society, Sir William Osler, in his second Lumleian lecture said "Had Heberden listened to my first lecture he could have remarked very justly 'Well! they have not got much ahead since my day'." In descriptive symptomatology we have not, and among 100 cases of angina pectoris there is no reason why Heberden should not have met all the important anomalies and complications. He had the good sense not to say much about the cause of the disease, and the good fortune to get very close to the truth in what he did say."

Contemporary with Heberden, were John Hunter, Edward Jenner and John Fothergill. These four were all in more or less intimate association with each other. It is of interest to note the possibility of discussion and conference between these men who, during the life of Heberden, cleared up this subject in such a way that little was added to it for another hundred years.

Hunter, himself, as everyone knows, was a victim of the disease. He was the greatest of the group, being ranked by Garrison along with Pare and Lister as one of the three greatest surgeons of all times. He was 45 years of age at the time of his first attack of angina, with which he was to be tormented for 20 years. Knowing his ailment he said, "My life is in the hands of any rascal who chooses to annoy and tease me." In a fit of anger at a meeting of the governors at St. George's Hospital, he had an attack, left the room and fell dead.

Heberden, a typical practitioner of that time, was 58 years old at the time of his first publication. He was a Cambridge graduate and an outstanding Greek and Hebrew scholar. His commentaries were written in Latin and were published in 1802, a year after his death. Of this it has been said—"The little book is one of the shining monuments of medical scholarship." Heberden died at the age of 91.

Fothergill, but two years younger than Heberden, was a Quaker, a successful and wealthy London practitioner, a friend of William Hunter. He was also a friend of Franklin and of the American colonies and in some measure aided in the founding of the Pennsylvania Hospital. He, in 1776, reported a fatal case which came to autopsy. The autopsy was performed

by Hunter whose description was rather meagre, the findings being in the main, negative, except as expressed in the last sentence as follows "The two coronary arteries from their origin to many of their ramifications upon the heart were become one piece of bone"

Jenner, the youngest of the four, was a favorite pupil of Hunter's and a close friend for many years. He was in practice at Berkeley in Gloucestershire and at this time was 27 years of age. Hunter, in the year 1776, the same in which he did the autopsy for Fothergill, had his second attack of angina. While he was convalescing at Bath he consulted Jenner about his ailment, who, in turn wrote to Heberden giving his diagnosis. The letter in part was as follows

"When you are acquainted with my motives I presume you will pardon the liberty I take in addressing you. I am prompted to it from a knowledge of the mutual regard that subsists between you and my worthy friend, Mr Hunter. When I had the pleasure of seeing him at Bath last autumn I thought he was affected with many symptoms of the angina pectoris. Though in the course of my practice I have seen many fall victims to this dreadful disease, yet I have only had two opportunities of an examination after death." He then describes the condition of the coronary arteries which he had noted at autopsy, adding, "As the heart, I believe, in every subject that has died of the angina pectoris, has been found extremely loaded with fat, and as these vessels lie quite concealed in that substance, is it possible this appearance may have been overlooked? The importance of the coronaries, and how much the heart must suffer from their not being able duly to perform their functions (we cannot be surprised at the painful spasms), is a subject I need not enlarge upon, therefore shall just remark that it is possible that all the symptoms may arise from this one circumstance

"As I frequently write to Mr Hunter I have been some time in hesitation respecting the propriety of communicating the matter to him, and should be exceedingly thankful to you, sir, for your advice upon the subject. Should it be admitted that this is the cause of the disease, I fear the medical world may seek in vain for a remedy, and I am fearful (if Mr Hunter should admit this to be the cause of the disease) that it may deprive him of the hopes of a recovery"

Referring to these autopsies at a later time, Jenner wrote to Parry

At this very time, my valued friend Mr John Hunter, began to have the symptoms of angina pectoris, too strongly marked upon him and this circumstance prevented any publication of my ideas upon the subject as it must have brought on an unpleasant conference between Mr Hunter and me

From the studies and observations, then, of these men originated the correlation of the symptoms of this condition, the introduction of the term "angina pectoris" and the idea that these symptoms had a very definite relationship to coronary sclerosis

Caleb Hillier Parry was in close association with this group for although he was six years younger than Jenner, they were boyhood and lifelong friends. He at one time spoke of Jenner as a friend of forty years, "acquired in the gay morning of my life". Parry was a famous practitioner of Bath, chiefly known by his account of exophthalmic goiter which antedated both Graves and Basedow. To him Jenner dedicated his work on

Vaccinia Parry's article on angina pectoris was written when he was 44 and two years before the death of Heberden. This monograph appearing in 1799 was without doubt the best discussion of the subject at that time and, in fact, for many years later. On the title page of the monograph appears the following "Inquiry into the Nature and Causes of the Angina Pectoris as they are Deducible from the Actual Symptoms and from Dissection." He then writes in his introduction "Such an inquiry will unavoidably involve me in the necessity of pointing out what appear to me the mistakes of some of my medical brethren in their nosological judgment of this disease. In a personal view this is a disagreeable task but when I consider that truth is the sole foundation of moral and religious virtue and therefore of happiness, my regard to personal delicacy is lost in a more general and greater obligation of public utility. In reality it is of little importance who is the discoverer of truths, however valuable. To mankind it suffices that the truth is actually known and the good obtained." One might add here that Parry gives Jenner full credit for the suggestion that angina pectoris arose from some heart changes, probably ossification or some similar disease of the coronary arteries.

There was a very important observation by Allan Burns published in 1809. This suggested the idea upon which the theory of intermittent claudication is based and the theory which is now quite generally held, namely, that the pain of angina pectoris is due to a relative ischemia. In his observations on "Diseases of the Coronary Arteries and on Syncope Anginosa" he speaks of the effect upon the leg of the application of a tourniquet, which would prevent satisfactory circulation, namely, the early fatigue of the muscle below the ligature. He likens that to the inelastic and incompetent coronary arteries and suggests it as a cause of the pain of angina.

After this publication of Burns there appeared to be no outstanding observations or publications about the coronary arteries until the time of Latham, 1845. This is the more remarkable because that was the period of the distinguished group of Irish clinicians, among whom were Adams, Cheyne, Colles, Corrigan, Graves and Stokes.

Latham was at one time physician to St. Bartholomew's, but gave up the position on account of his health. Later he published a book—"Diseases of the Heart"—based on his hospital lectures. Stokes said of this "The two concluding lectures of Dr. Latham should be carefully studied, not only as bearing on the disease in question, but as fine examples of medical writing." These last two lectures of Latham just missed being epoch making. Much that he wrote cannot be paraphrased without a definite loss of picturesqueness and charm of expression and in consequence will be quoted.

Angina pectoris from the time it was first described by Dr. Heberden has always had a large share of attention paid to it. Much has been written about it, and well written, by some of the best men in our profession. But it is still of very doubtful

pathology, and its pathology has little chance of being further illustrated, unless there be a clear agreement among us what we are to understand by the thing itself

I believe that the definition, which has been given, includes all that is proper to angina pectoris and excludes all that is not, and that it consists essentially of pain in the chest and a sense of approaching dissolution. Not from the absolute constancy but from the very great frequency of its occurrence there is one more element, which has a claim to be considered almost as a part of the disease. Its very peculiarity forces it upon our notice. It is an extension of the pain to one or both arms, most frequently to the left and stopping at the elbow, sometimes to the right, and sometimes to both, and sometimes reaching to the fingers.

But what is angina pectoris? Its symptoms, striking and definite as they are, do not carry their own interpretation along with them. They tell neither whence they are nor what is their efficient cause. (To that end) we must gain what help we can from the many circumstances which various clinical histories and various dissections have disclosed and there are plenty of such histories and dissections upon record. I have both seen many and read many. But all the cases which one sees or reads of a particular disease do not necessarily add to our knowledge. They may make the knowledge which we have, more familiar without augmenting it. They may freshen our experience without enlarging it. Yet some one case out of many from peculiar circumstances belonging to it may teach us something, which we did not and could not learn from all the rest.

Thus, I have three cases of angina pectoris to report, two falling under my own observation and a third coming to me upon the best authority, which added something at least to my knowledge of the disease.

He then reports three cases in detail. All came to autopsy. One of these was Thomas Arnold of Rugby, who with his father, William Arnold, and his son, Mathew Arnold are frequently referred to as illustrating the familial tendency of the disease. After the detailed accounts of these cases he writes

Here then are three cases of angina pectoris. In the first we have death in a fortnight, in the second death in ten days, in the third death in less than three hours, from the first seizure. Now circumstances cannot be conceived more favourable than those which these three cases present for ascertaining the connection between symptoms declared in the living, and changes of structure found in the dead. The symptoms were essentially the same in all. They were few and striking and constituted of actions and sufferings which manifestly could, and manifestly did, cause death. They were also uncomplicated, no other symptoms interfering to spoil the simplicity of each case, before death arrived.

There are no cases upon record in which death followed the first accessions of angina pectoris so rapidly, as in those three which I have related. And if the disease essentially proceeds from any material element which morbid anatomy can detect, these were the cases in which to find it. You know what *was* found in these cases. Unfortunately for the success of our inquiry, not the same thing in all. Extreme muscular attenuation in two, and muscular attenuation of less degree conjoined with ossified coronary arteries and an ossified aorta in the third. But had there been simple ossification of the coronary arteries in all or simple muscular attenuation in all, yet could neither one nor the other be regarded as the proper efficient cause of angina pectoris. For though one or both are often traceable among the complex forms of disease found in those who die at later periods, yet one and both are often entirely absent. What then have these cases, so new and interesting in their details, taught us after all? They have taught us that angina pectoris has a greater, an earlier, and more instantaneous power to kill than it was ever hitherto thought to have, and they

have (in this way) enlarged our knowledge of its clinical history, and have thus enabled us perhaps better to understand its real nature

One cannot escape the conviction that these three unusually rapidly fatal cases so well described and discussed by Latham were what is now so easily and often recognized as coronary thrombosis. His differentiation from the angina of effort of Heberden was complete. He even went so far as to put them in a class by themselves and only failed in that he failed to discover the fundamental condition which made them different. Knowing the ease with which thrombosis in a coronary artery may be overlooked, this failure is easy to understand.

In Stokes' book on "Diseases of the Heart and Aorta" in 1854, a book of 600 pages, he allows 8 pages for the discussion of angina pectoris. Most of that discussion refers to the ideas of Heberden, Parry and Latham. He writes

Upon the whole, we may conclude, that the special group of symptoms described as angina pectoris by Heberden, Parry, Percival and Latham, is but the occurrence, in a defined manner, of some of the symptoms connected with a weakened heart. *Obstruction of the coronaries may or may not be present, and is probably not infrequent, but as the cause of angina, its action is remote, and its existence unnecessary.**

Majoi, in his "Classic Description of Disease," gives the credit to Adam Hammer for having first made the diagnosis during life of coronary thrombotic occlusion. Hammer was a German who apparently for political reasons left Germany after the revolution of 1848 and came to this country and, with some associates, established a medical school here. Briefly, the case which Hammer reports and which was reported in *Wiener Medizinische Wochenschrift*, 1878, was as follows. He was called by one of his younger colleagues to see a patient who was apparently in extremis, and after consideration of the history, the symptoms and signs, he told his colleague at the bedside, that these symptoms could only be produced by thrombotic occlusion of at least one of the coronary arteries. The colleague replied, "I have never heard of such a diagnosis in my whole life" and Hammer writes "I answered, 'Nor I also'". Subsequent autopsy showed that the right sinus of Valsalva contained a thrombus which had ultimately completely shut off the lumen of the artery.

This, however, is not at all the type of occlusion which is now so commonly seen in which the thrombus is formed somewhere within the course of the artery, and which is usually due to arterial disease. To George Dock in 1896 has long since been given the credit for having observed and discussed a case of this type and having ventured the diagnosis while the patient was living. He saw the patient about a week after the onset of cardiac pain. His description of the onset and the history at that time was about what one notes now in an ordinarily severe case. The sounds were faint but clear. There was a loud double friction sound at the apex region. There were loud moist râles in the lungs. After giving an

* Italics not in the original

account of the symptoms and signs, he writes "The diagnosis was myomalacia following coronary sclerosis with secondary pericarditis. This was based on the history of increasing dyspnea and heart pain without evidence of disease in the lungs or kidneys, or other (valvular) disease of the heart, the history of the acute attack indicating infarction, and the acute onset of pericarditis without other cause." The same day against orders the patient got out of bed to go to the toilet and suddenly died. The autopsy showed a thrombosis of the descending branch of the left coronary and a resulting infarct.

Osler's "Angina Pectoris and Allied States," a volume of lectures delivered in 1896, is rich in references to the symptoms and pathological findings of coronary artery disease, and it is not easy to understand why the correlation of these signs, symptoms and findings was not made earlier. For example, in discussing the coronary arteries and speaking of the descending branch of the left coronary artery, he says

"This anterior branch is the important one in the morbid anatomy of the coronary arteries, since it is by far the most frequently found seat of extensive sclerosis or of embolism or thrombosis. It may be called the *artery of sudden death*." He writes further on—"The effect of plugging of the artery is the production of what is known as an anaemic infarct, a well-recognized pathological condition, the consideration of which need not detain us. A very important matter relates to the effect of plugging of the coronary arteries upon the heart-beat, the contractions become of the type known as fibrillary, and it is difficult or impossible to get the organ to resume the ordinary coordinated beats, though experimentally this has been done, even after fibrillary contraction has been established."

In demonstrating a pathological specimen, he said "In this anterior coronary artery you see a firmly adherent thrombus, which completely occludes the descending branch, to the lumen of which it is firmly attached. It was taken from a man about fifty years of age, who had mitral-valve disease and had a good deal of cardiac dyspnoea. Early one morning he was seized with a severe pain about the heart and shortness of breath, and died in a very few moments. No doubt the sudden death was due to the blocking of the anterior branch of the left coronary artery by the thrombus."

"When the occlusion has persisted for any length of time before death the condition of anaemic necrosis may be found. The man with a fresh thrombus in the anterior branch of the left coronary artery probably died in a paroxysm of angina, but he had not had previous typical attacks. As I will tell you later on, the affection is rare in hospital practice so that we do not have opportunities of making the inspection of the bodies of persons who have died of the disease." With reference to its rarity in hospital practice he elsewhere said "During the ten years in which I lived in Montreal, I did not see a case of the disease either in private practice or at the Montreal General Hospital. At Blockley (Philadelphia Hospital) too, it was an exceedingly rare affection. I do not remember to have had a case under my personal care. There were two cases in my service at the University Hospital. During the seven years in which the Johns Hopkins Hospital has been opened, with an unusually large 'material' in diseases of the heart and arteries, and with many cases of heart pain of various sorts, there have been only four instances of angina pectoris. You will find the statement in Fagge's Practice (third edition, vol. II, p. 26) that 'the writer has never seen classical angina in hospital practice.'"

In a large consultant practice it was more frequently seen. For instance, Dr. Balfour at that time had analyzed 98 cases which came under his observation in 10 years. Osler said that his own experience had embraced a series of 60 cases, 40 of which he considered to be true angina.

The views and arguments currently put forward as to the reasons for the real or apparent greater frequency of coronary thrombosis at the present time will not be discussed here.

The mechanism of instantaneous death has always been a problem and a problem which has had much discussion and various explanations. Lately we have come to believe that in many cases in which death in coronary artery disease is instantaneous it is due to ventricular fibrillation. So long as 40 years ago when these lectures were written, Osler made a significant suggestion in speaking of Kronecker's coordination center, of which the "knowledge is still very indefinite." He said

"I have seen Kronecker perform the experiment, and certainly when the point in the dog's heart is pricked—it is situated about the lower limit of the upper third of the ventricular septum—the organ becomes paralyzed in a state of fibrillary tremor, from which it does not recover. This point is within the area of distribution of the anterior coronary artery, the vessel oftenest found plugged by thrombus or embolus in cases of sudden death."

In another lecture he says, "It does not fall to the lot of many physicians to witness the sudden death in angina but there are observations to show that the pulse beat and the heart stop abruptly. Dr. Thayer (who was present in one instance) tells me that the death seemed instantaneous—the pulse ceased *at once* and there were no further heart beats. As I have before remarked, the mode of death resembles that produced by Kronecker's heart puncture."

In still another lecture speaking of these cases of sudden death, he said, "An explanation of the awful suddenness is probably to be found in the arrest of the heart in fibrillary contractions such as take place experimentally in animals after ligation of a coronary vessel."

Osler describes two cases under the heading of "Rapidly Repeated Attacks of Angina over a Period of Days or Weeks, with the Development of a State of Cardiac Asystole." These he apparently considered belonging in the class of status anginosus. One lived six days, the other 19. The perusal of the history leaves no doubt in the mind of the reader that these two cases were instances of coronary thrombosis. He remarked that he had seen but two cases of this type.

In discussing Allan Burns' Theory, he said

"Very different to this relative ischaemia of the cardiac muscle must be the condition following the blocking of a large branch by a thrombus or an embolus*. The resulting anaemic infarct, if at all extensive, must cause not alone great weakness of the cardiac muscle, but at the site of the lesion the smooth uniformity of the waves of contraction must be seriously interrupted. This cardiomalacia may lead to rupture of the wall of the ventricle (eleven cases in Huchard's collection of autopsies) or *may cause pericarditis*†. While the anaemic infarct is a well-recognized lesion in fatal

* In this sentence Osler differentiates between angina pectoris and coronary thrombosis.

† Italics not in the original.

cases of angina pectoris, it must be remembered that a paroxysm of pain is really a rare complication of this not infrequent change. It is interesting to note that the scars of infarcts have been found years after recovery from attacks of angina."

Again we have an illustration of how long a time it sometimes takes for a well established medical fact to be recognized and accepted. It is no doubt true that in Latham's time, postmortem examinations were not nearly so carefully made. Pathological processes were not so easily recognized or so well understood but we know that at the time of Osler's writings, these processes were well understood and that autopsies were carefully made and that Osler was an extraordinarily well trained pathologist and clinician. While Osler put these cases of coronary thrombosis in a group by themselves, his experience with them at that time was so limited that it apparently seemed to him as it did to many others for a number of years that thrombus formation in a coronary artery with a resulting infarct was simply an incident in the course of coronary disease which, as a rule, immediately preceded death and was not of particular importance clinically. This in the face of the fact that he makes the definite statement that healed infarcts were frequently found post mortem.

It was another 16 years before Herrick's observations were published indicating that thrombosis may occur and recovery take place with subsequent years of satisfactory life. So far as the clinical diagnosis of sudden thrombotic obstruction of the coronary was concerned, it remained for Herrick to bring order out of the confusion. In his paper of 1912 he described most of the symptoms which we now recognize as being associated with thrombosis: persistent pain, ashy pallor, sweating, nausea, vomiting, abdominal symptoms which might be confused with abdominal surgical conditions, râles in the lungs, arrhythmia, feeble pulse, dyspnea, cyanosis, pericarditis, fever, as well as some changes in the electrocardiogram. This paper was read before the Association of American Physicians, published in the *Transactions* and also in the *Journal of the American Medical Association*. However, scant notice was taken of the subject even then until after his second paper, six years later, in which he reported more cases and emphasized again what he had before published. His observations and suggestions did much to take the condition out of that group of fatal diseases in which the diagnosis is only of academic interest, for he emphasized particularly the opinion that many cases of thrombosis were mild and that recovery frequently did take place. From that time interest in the subject became gradually more widespread until familiarity with the disease became quite universal.

After all, the more familiar one becomes with angina pectoris and coronary thrombosis, the more one realizes that—if we are right in the prevailing theory of what angina pectoris is, namely that it is due to the relative ischemia of the heart muscle—these two conditions would seem to be but different manifestations of the same thing, having as their common basis

coronary artery disease In one the obstruction develops slowly, is progressive, but is partial, while in the other it is sudden and complete The latter condition is a very common termination of the former The important reason for their differentiation is that the two conditions require very different treatment Probably in no other malady does the failure to make a correct diagnosis so frequently contribute to a fatal outcome, as in coronary thrombosis

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EFFECTS OF TREATMENT ON RADIUM AND CALCIUM METABOLISM IN THE HUMAN BODY^{*}

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IN 1924 Blum, a dentist,¹ and in 1925, Hoffman¹ suggested that radium produced necrosis of the jaw. Our knowledge of the pernicious effects of stored radium salts in human beings dates essentially from the publications in 1925 of Castle, Drinker and Drinker² and also Martland³ when necrosis of the jaw in workers who had absorbed radium salts was reported and discussed. Since that time, increasing numbers of similar cases have been recorded. Other abnormal clinical results of radium have been the appearance of severe anemias as well as a high percentage of osteogenic sarcoma, first described and discussed by Martland,³ in 1931.

In the intervening years, several interesting investigations have been reported regarding the storage and excretion of ingested radium salts, and have been summarized by Evans.⁴ Thomas and Bruner⁵ gave radium chloride subcutaneously to eight rats. These animals developed a secondary anemia and the bones subsequently showed a hyperplastic bone marrow in the middle of the shaft while an aplastic marrow was found toward the epiphyses. We found a similar appearance in the bones of one human case (C I). Only 25 per cent of the injected radium was found in their animals after an average of 21 weeks of injections, followed by 57 days of rest. Approximately 50 to 65 per cent of the injected radium was eliminated one week after the first injection, whereas later average elimination of radium, established for two of the animals, was estimated to be 0.6 per cent per week.

Schlundt and Failla⁶ in 1931 studied radium excretion in humans and found that over 90 per cent of radium taken by mouth is eliminated within five days—yet the daily rate of excretion long after exposure was but a small fraction of the total still stored in the bones.

In 1926 a new treatment of lead poisoning was recommended by Aub and Minot,⁷ based on the observation that lead in the body parallels the calcium metabolism, and utilizing the available methods of influencing calcium in the bones to control the circulation of lead. In 1929, Flinn and Seidlin⁸ reported that such "deleading" therapy with parathyroid extract caused an increased excretion of radium. In 1931, Flinn⁹ reported excellent re-

^{*} Received for publication September 27, 1937.

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This is No. XXIII in the series of papers entitled "Studies of Calcium and Phosphorus Metabolism."

sults with the use of large doses of viosterol. No collection of excreta was made, but electroscopic tests of the patient were made both by gamma ray method and by radio-activity of the expired air, according to the method described by Schlundt, Barker and Flinn.¹⁰

These findings of Flinn's were questioned by Craver and Schlundt,¹¹ who studied four radio-active girls. They were given a low calcium diet and injections of parathyroid extract starting with 10 units every other day and increasing to 50 units a day. They were then given three weeks of high calcium diet with viosterol up to 30 drops a day, followed by three weeks of low calcium diet plus parathyroid extract, and then again given a high calcium diet with viosterol. Only the last three days of each period were analyzed. The results showed an increase of radium excretion in all the analyses with low calcium diet plus parathyroid medication, and equivocal effects from viosterol. They arrived at the conclusion that neither the administration of parathyroid extract nor of viosterol causes a substantial reduction in the total deposited radium.

As with nearly all excellent pioneering work, the technics used in these earlier investigations may be improved. Flinn gave no figures of excretion rate of radium salts. Craver and Schlundt had the patients prepare their own diets and collect their excreta in their homes, but also alternated low and high calcium diets, which reduces the influence of the treatment on stored heavy metals subsequent to the high calcium diet. Neither the parathyroid extract nor the viosterol was adequate greatly to increase calcium excretion, indeed, the viosterol was given probably only as an aid to calcium absorption.

Because of these divergent results, and because of the greatly improved methods available to us, both in metabolic technic and radium analyses, we decided to reinvestigate this problem of radium excretion and of the treatment in cases of stored radium.

Methods The three patients were put on our routine metabolic regime,¹² and were kept in the hospital during their study. The preparation of their diets and their general management was done with the greatest possible accuracy. Collection of their urine and feces was repeatedly checked in our usual routine manner. The patients were most cooperative, and ate their full diet daily, and there were no known errors made in the collection of excreta throughout their stay in the hospital. The urines for three days were measured and mixed, and an aliquot preserved with hydrochloric acid for calcium analysis. The preparation of the remainder of urine for analysis of radium was the entrainment reaction used by Fairhall¹³ for the precipitation of lead, which was found effective for the separation of radium. The precipitate of alkaline phosphates was subjected to wet digestion by nitric acid, dried, and extracted with hydrochloric acid. The entire feces for each period were mixed and digested on the steam bath with nitric acid until a clear solution was obtained. This extract was used for both radium and calcium determinations.

Calcium determinations were made by the method of Fiske and Logan¹⁴ Radium determinations were made by the method of Evans¹⁵ Determinations of total radium in the body, as well as expired air samples and blood samples were also made by his methods¹⁶ The chemicals used disclosed no measurable evidence of radio-activity except the nitric acid which contained not more than 1.5×10^{-12} gram of radium per 100 c c, an amount which would not affect the results of our analyses

The excretion of radium has been shown to be very rapid at first and then eventually to settle down to a very small excretion which is but a small part of the remaining stored radium Schlundt⁶ found that when he drank radium in water he excreted over 90 per cent of the radium in the subsequent five days Seil, Viol and Gordon,¹⁷ and Schlundt, Nerancy and Morris¹⁸ found that the elimination of soluble radium salts was rapid the first week after injection but decreased to less than 1 per cent per day in the next few weeks In two chronic cases, 12 years after exposure, Schlundt and Failla⁶ found an excretion of only 0.002 to 0.005 per cent per day, or about 0.1 per cent per month High initial excretions were also obtained in rats by Thomas and Bruner⁵ These findings are well confirmed in our observations One of our patients (Pt 3—R. L.) had inhaled radium only seven weeks before entering the hospital Though he was harboring only about 4 per cent of the amount that is stored in our more chronic cases yet his rate of radium excretion was approximately six times greater than theirs and had been even higher three weeks previously (table 4) The explanation for this appears to depend largely upon the distribution of radium in the body It has been shown that lead,¹⁹ thorium B,²⁰ polonium,²¹ and radium,⁵ itself, are scattered through the soft tissues as well as in the bones soon after administration In the case reported by Cameron and Viol,²² though they did not analyze bone, radium was still widely distributed in the rest of the organism 3½ months after intravenous injection Gradually, these abnormal metals are excreted or stored predominantly in the bones Recent work by Calhoun, Hudson and Axel²³ has shown a gradual change in distribution in the bone, itself At first a heavy metal is stored largely in the bone trabeculae, there being from 11 to 16 times as much per gram in the trabeculae as in the cortex of the bone During the following months there is a redistribution and the concentration becomes equal in both trabeculae and cortex Because the cortex is far heavier than the trabeculae, this means that most of the radium is stored in cortical bone This distribution indicates an explanation for the variation in radium excretion The wide distribution in soft tissues and then the accumulation in the bones implies considerable circulation in the blood and therefore a chance for rapid excretion The first large surge in the excretion of these inorganic salts are readily deposited and are easily removed and then a continued though less rapid excretion When the radium finally accumulates in the cortex, it is to be expected that excretion would be relatively poorly influenced by therapy.

The Route of Excretion Seil, Viol and Gordon¹⁷ and Schlundt and Failla⁶ showed that 90 per cent of radium is excreted in the feces. Our experience agrees roughly with this figure. We find the radium in the feces varies with that found in the urine, even during periods of artificially accelerated excretion. Thus in patient 3 (R. L.) the fecal elimination is 96 to 99 per cent of the total excretion in all the periods, in patient 2 (E. C.) it is 94 to 99 per cent in all but two periods (19 and 21), and in patient 1 (M. H.) it varies between 88 to 94 per cent. This is a constant value as judged by usual metabolic variations, indeed far more constant than found for other inorganic salts. Lead is largely excreted in feces and nearly all the increase from therapy appears there.²⁴ Mercury, however, is excreted more in the urine than the feces, though a low calcium diet plus ammonium chloride increases fecal excretion ten fold and urinary excretion only three and one-half times.²⁵ None of these metals are normal constituents of the body except in minimal concentrations in contradistinction to calcium, which is fairly closely related to them chemically. When stored calcium is excreted, on our low calcium diet without medication, about two-thirds of it appears in the feces, but nearly all of the increased excretion induced by therapy (excepting that produced by thyroid) appears in the urine. Therefore, there is no constant relationship between urine and fecal excretion ratios in different heavy metals. What induces fecal excretion and what part of the intestinal tract is involved is not well known. It has been shown that lead can be excreted in considerable amounts in the bile.⁷ Salant and Meyer²⁶ found that radium excreted in feces came particularly from the liver and small intestines. We have had an opportunity to get some further information in regard to radium and biliary excretion. A patient (C. I.) who had $5 (\pm 1) \times 10^{-6}$ gram of radium in her body was found at autopsy to have a good many, though light gall stones. The results of the analyses of one-half (1.83 gm.) of the total sample disclosed that there was 0.032 gram of calcium and 0.022×10^{-9} gram of radium per gram of gall stones (table 3). It is thus clear that radium, like lead, may be excreted through the bile into the intestinal tract. The ratio Ra/Ca is lower in the gall stones than in the bones (see table 3), which may be accounted for by the relatively small concentration of radium and hence only a partial precipitation in bile. Obviously, this does not permit a quantitative interpretation of the concentration or rate of radium excretion.

From these observations, it appears that radium excretion is analogous to that of lead and that (1) approximately 90 per cent of excreted radium appears in the feces, both with normal and stimulated excretion and (2) that some of the excreted radium occurs in the bile, for radium was found in the gall stones of a patient with radium poisoning.

Results of Treatment The problem of the treatment of radium poisoning was studied in three individuals who had received their store predominantly by different routes: (1) intravenous, (2) by mouth, and (3) by inhalation. Two of the patients represented chronic effects with obvious

symptoms, while the third had only recently absorbed a small amount of radium without deleterious effects

CASE REPORTS

Patient 1 (M H) had received an undetermined amount of radium intravenously ten years before entrance to the hospital. This was given as therapy for a minimal amount of chronic arthritis, which had not subsequently progressed. On admission she was suffering from severe necrosis of the jaw of two years' duration. Eight months before entrance she had devoted six weeks in her home to a low calcium diet plus ammonium chloride and thyroid extract. Therefore, this was her second course of treatment, and it is to be expected, from our experience with lead, that the results obtained in the hospital would be of lower magnitude as a result of this previous therapy. At the end of her hospital stay, she had 15.2 (± 1) micrograms of radium stored in her body. This was determined by adding 8.5 micrograms of radium determined as radium C gamma rays plus 6.7 micrograms found as radon in an analysis of expired air (1.7×10^{-10} Curies of radon per liter) (table 5)

TABLE 1

Patient 1, M H Total Radium in Body = 15×10^{-6} gm
(Intake and Output in 3-day periods)

Period	Diet and Medication			Calcium in Serum	Calcium Excretion	Radium Excretion	
					Urine	Urine	Feces
				mg %	gm	$\times 10^{-9}$ gm	$\times 10^{-9}$ gm
1	Low calcium diet only (0.27 gm Ca)			9.9	0.45	0.17	2.5
2				9.8	0.39	0.16	2.1
	Thyroid extract	NH ₄ Cl	Parathyroid extract				
	gr	gm	units				
3	9	18	1200	11.3	0.32	0.37	2.5
4	9	18	900	10.3	0.51	0.60	4.9
5	9	18	1200	11.3	0.56	0.27	5.5
6	9	18	1500	11.8	0.28	0.99	8.4
7	9	19.5	1500	11.5	0.96	0.82	7.2
8	9	22.5	1500	12.2	1.68	1.94	
9	9	22.5	1200	13.1	1.40	1.70	16.4
10-11	9	22.5	1200				
12-13		18	1200				
14		18	1200	12.5	0.92	0.78	8.2
Second Admission—After 5 weeks on low calcium diet							
15	High Ca diet (5.0 gm Ca)			10.0	0.16	0.34	2.5
16	Diet plus Ca gluconate (10.0 gm Ca)			11.0	0.52	0.21	2.3

Without medication she excreted an average of 0.8×10^{-9} gram of radium per day which is about 0.005 per cent of her total body radium. From the laboratory data as disclosed in table 1, it is clear that the use of a low calcium diet plus ammonium chloride, plus thyroid and parathyroid extracts⁷ increased her radium excretion six to eight fold during the period of maximum medication.

The control period, obtained five weeks later, corresponded to the original output of radium. It must be pointed out, however, that the rate of excretion of these chronic cases of radium poisoning is of an extremely low magnitude. In spite of the fact that this medication definitely increased the radium elimination, the total increase remained but a small fraction of the total radium which was stored in her bones, for she only excreted approximately 0.1 microgram more than would have been eliminated without this therapy. This represents an increase of only two-thirds of 1 per cent above her normal rate (0.15 per cent) of elimination per month. Yet there was a striking improvement in the condition of her mandible. Before treatment, the necrosis of bone had progressed during two years to such an extensive bone destruction that her very able dentist had told her not to yawn for fear that she would fracture her jaw. Following this therapy, the sinuses in the bone promptly disappeared and the bone healed into a respectable and quite normal-looking jaw.



FIG 1. Roentgenograms of the same area of mandible of Patient 1 (M. H.). I Taken before treatment, showing necrosis of mandible. II Taken nine months later, and one month after second course of treatment.

The roentgen-ray photographs indicate this striking change (Figure 1). In the two years which have followed this observation, this condition has continued well, except for a single, very small and superficial spicule of bone which remains in the gum. This striking improvement occurred in spite of the fact that only a small percentage of the total radium stored in her body could have been eliminated during the course of this treatment.

Patient 2 (E. C.), a woman of 30 years, was a dial painter from the time she was 16 years of age. From her industrial surroundings it is obvious that most of the radium which she had stored was accumulated in the first seven years of her exposure, and that in the last seven years exposure must have been slight. This is based upon the fact that cleanliness of the

factory was greatly improved, and the technic of applying paint was changed from mouth-pointed brushes to the use of sharp glass pencils. The evidence for early accumulation of radium in this patient is also shown in her bones.

From roentgen-ray pictures it may be seen that obvious damage had been done before the epiphyses at the head of the humerus and the femur had united, with the result that this area of the bones shows distinct lesions.



FIG 2

FIGS 2, 3, and 4. Roentgenograms of Patient 2 (E. C.). These disclose the abnormal epiphyses, and varying degrees of bone destruction and proliferation.

and abnormal union (Figures 2 and 3) It is well known as a result of the observations by Vogt²⁷ and Park,²⁸ and our own analyses²⁰ that the heaviest deposit of lead in the bones of children is at the epiphyses It is

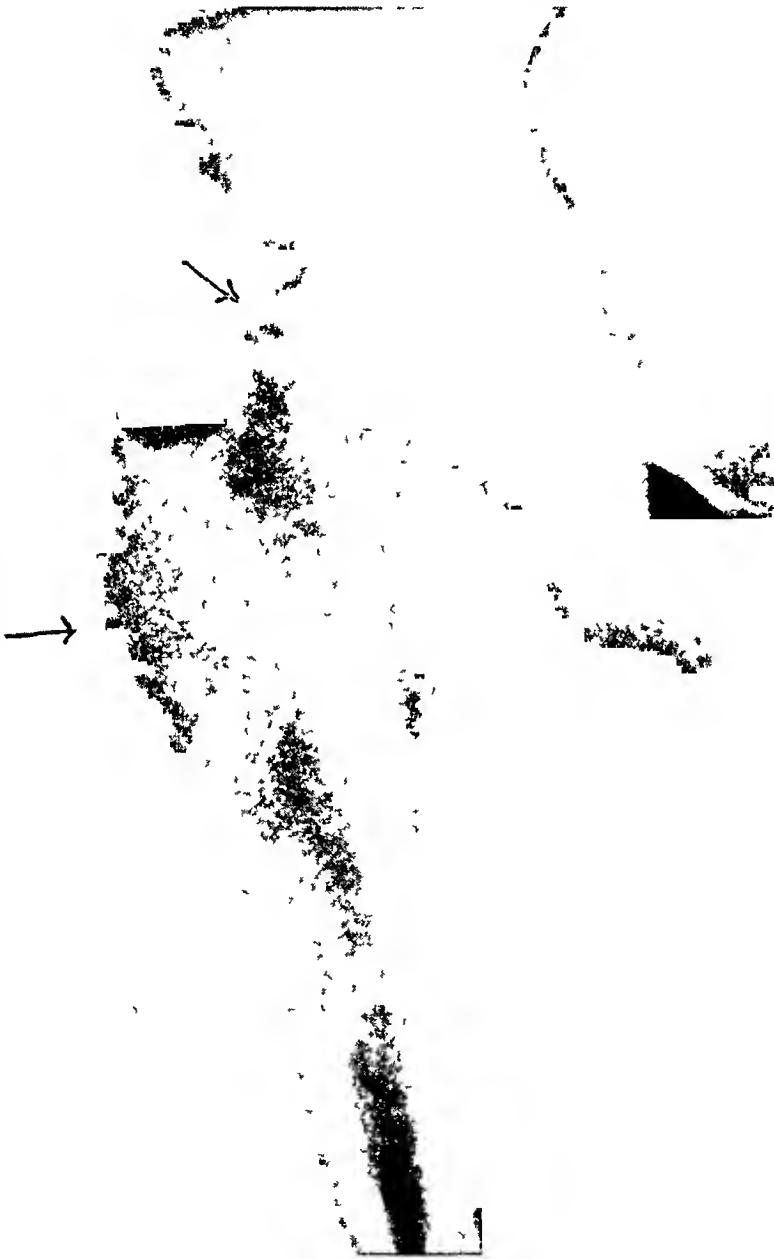


FIG 3

highly likely that radio-active salts have a similar predilection for epiphyseal areas, because in rats they are also the areas most heavily impregnated with thorium in the observations of Behrens and Baumann²⁰ and with radium as judged by the picture published by Thomas and Bruner⁵ (their figure 15)

This is also true of radio-active lead in dogs²³ It, therefore, seems quite clear that the bone lesions in this patient represent deleterious radium effects obtained from a high concentration of radium in the ununited epiphyses. As the upper epiphyses of the humerus normally unite at 20 years of age, and of the femur at 18 years, one must expect that its effect occurred before this age.



FIG 4

Here, then, is a patient who had been exposed to radium for 14 years, with most of the exposure in the first seven years. The deleterious physical effects which she manifested obviously dated back to this early exposure. One cannot say, however, that she was entirely free from exposure during the last seven years. Very careful calibration of the radium in her body disclosed that she had $18 (\pm 1) \times 10^{-6}$ gram of radium stored in her body. Gamma ray measurements indicated that the radium was distributed non-uniformly, in the manner characteristic of radium poisoning.¹⁶

This patient was an excellent subject for metabolic study, for she co-

TABLE II
Patient 2, E C Total Radium in Body = 18×10^{-6} gm
(Intake and Output in 3-day periods)

Period	Diet and Medication				Serum Values		Calcium Excretion		Radium Excretion	
					Ca	P	Urine	Feces	Urine	Feces
					mg %	mg %	gm	gm	$\times 10^{-3}$ gm	$\times 10^{-3}$ gm
1	House diet								0 07	2 7
2	House diet								0 17	2 7
3	Low Ca diet only (0 31 gm Ca)				10 2	4 6	0 22	0 29	0 04	2 8
4	Thy- roid ext	NH ₄ Cl	Para- thy- roid ext	Mg gluconate						
	gr 6	gm 12	units	gm			0 47			3 9
5	6	15	750				0 47	0 19)		5 9
6	6	15	900		10 1	2 7	0 46	0 20)		5 5
7	9	15	1500		10 3	2 4	0 54	0 17		5 9
8	9	15	1500		10 1	3 3	0 72	0 14		6 2
9	12	15	1800		9 9	3 5	0 63	0 12)	0 25	5 8
10	12	18	2100				0 79	0 11)	0 35	6 8
11	12	18			9 6	3 4	0 61			8 2
12	12	18			9 6	3 6	0 70	0 10)	0 52	8 1
13	12	18					0 79	0 10)		10 2
14	12	22 5			10 0	4 1	0 71			6 8
15	12	22 5					0 74	0 14)	0 53)	14 4
16	12	22 5					0 84	0 15)	0 53)	10 0
17	12	22 5		51	10 0	3 9	0 81	0 21		10 8
18	12	30		51	9 6	3 6	0 87	0 21		10 6
19	12	30		51	9 9	3 7	1 07	0 15	1 40	9 9
20	12	30		76 5			0 97	0 27	0 62	12 0
21	12	30		76 5			0 96	0 21	0 86	9 3
22	Low calcium diet— No medication				10 2		0 40		0 28	9 4)
23							0 19	0 15	0 22	9 4)
24							0 14	0 16	0 13	(7 6
25							0 14	0 17	0 11	(7 6
26	Ergosterol— 6 drops						0 17	0 14)	0 15	
27	Ergosterol— 9 drops				9 9	5 4	0 17	0 14)	0 13	
28	Ergosterol— 9 drops				10 0	5 9	0 15	(0 09		9 4)
29	Ergosterol—10 drops				10 5	5 6	0 18	(0 08	0 15	9 4)
30	Ergosterol—12 drops				10 5	5 4	0 23	0 05)		8 2
31	Ergosterol—18 drops				10 2	5 6	0 30	0 05)	0 19	7 6
32	Ergosterol—30 drops						0 29	(0 04	0 15	7 3
33	Ergosterol—30 drops				10 2	6 1	0 27	(0 04	0 25	10 0
34	Low Ca diet only				10 2	6 0	0 34	0 03	0 25	8 7
35	High Ca diet only (4 1 gm Ca)				10 7	5 9	1 46	lost		
36							1 42	1 72	0 15	6 3
37					10 2	6 0	1 26	1 77	0 24	4 1
38					9 9	5 2	1 25	2 18	0 16	5 6
39							1 21	2 06	0 12	4 0

Bracketed figures represent combined analyses

operated very well in every way. We were, therefore, able to obtain a very complete and accurate metabolic observation. For the first two periods she was on a normal house diet, and at this time her normal rate of radium excretion was determined, and found to average 0.9×10^{-9} gram per day which is approximately 0.005 per cent of the total radium in her body. From then on the course of her metabolic studies is indicated in table 2.

The results of the observation indicate that the various metabolic procedures which we used caused an increase in radium excretion roughly parallel to the calcium excretion. A low calcium diet, plus thyroid extract, and the acid-producing salt, ammonium chloride, definitely raised the radium excretion just as it did in Patient 1, and throughout the various periods of medication the radium excretion remained between three to four times the control values.

The addition of magnesium gluconate to therapy was accompanied by a slightly increased amount of ammonium chloride in order to partially neutralize the alkaline magnesium gluconate. In spite of the reduced acidity of this regime, both radium and calcium excretions were elevated by the magnesium gluconate, and this was the only therapy which seemed to increase the relative proportion of radium excreted in the urine. This finding corroborates the similar finding of Tibbetts and Aub³⁰ of the effect of magnesium ingestion on calcium excretion.

The radium excretion, however, does not always parallel the change in calcium excretion, thus in the periods of no medication (23 to 25), the calcium excretion had returned to a very low level, but the radium excretion continued relatively high. In the last four periods (36-39), in which a high calcium diet was given, in spite of a definite storage of calcium at that time, the radium excretion still remained well above its original level. This may be accounted for by the fact that vitamin D has a metabolic effect which certainly lasts a month. The fact remains, however, that the excretion of radium varied much more sluggishly than that of calcium. This may well be due to the fact that heavy metals, when liberated from bone, are stored in various soft tissue organs such as the liver, lungs, and kidney. When such a storage occurs, one would expect an elevated excretion to continue just as it does in acute cases.

Several other phenomena occurred in this observation which are of importance. This patient did not respond at all to very large doses of parathyroid extract (Lilly), either in the blood calcium level or in the rate of calcium excretion. This can be seen by comparing the calcium excretion in periods 8 to 10 with that in periods 11 to 16. Nor was there any dramatic change in radium excretion during this medication, inasmuch as the radium progressively increased in excretion throughout periods 6 to 16. We are certain that this batch of parathyroid extract was potent, for it was retested on dogs both by Eli Lilly Company and by us, and a satisfactory elevation of blood calcium was obtained. Why then did this patient not respond except by a slight lowering of blood phosphorus level? A possible

explanation is that her osteoclasts were sufficiently damaged so that they were unable to respond to the normal stimulus of parathyroid extract, and were, therefore, unable to liberate bone salts. Further evidence of damage to bone cells is suggested in this patient by the low level of phosphatase in the blood stream (normal is 0.15 Kay units) which would suggest that the osteoblasts were relatively inactive. The phosphatase determinations of this patient (0.06 Kay units) did not vary throughout the observation. In spite of this suggested injury to her bone cells, however, this patient was still able to store calcium at a rapid rate in the first periods of high calcium diet toward the end of her observation.

Another medication to which there was no dramatic response was very large amounts of activated ergosterol, of which she was given as much as 750,000 international units in three days, without effect on her blood calcium level. The only response to these high doses was a shift in her calcium excretion from feces to urine, indicating an increased absorption of calcium from the bowel. The storage or liberation of calcium in the bones was not affected. However, this cannot be said to be definitely abnormal in spite of the big doses, because C. I. Reed³¹ also did not get constant changes in blood levels from similar doses, but it is suggestive evidence confirmatory of that obtained with parathyroid extract. All that can be said of its effect on radium excretion is that this remained at the higher levels (table 2) established by the previous therapy. In summary, one may say that the methods of therapy which we used did increase the rate of radium excretion but the amount of radium which was withdrawn in this advanced case was insufficient to definitely lower the determinations of total stored radium in the body. In this regard the results agree with our first case and with the conclusions of Craver and Schlundt.¹¹

Is Radium as Easily Excreted as Calcium? It would be of interest to know whether the radium which is excreted corresponds with its relative ratio to calcium in bone, in order to determine whether therapy is more efficient in eliminating either the normal body constituent, calcium, or the abnormal radium. What one wants to know is the Ca/Ra ratio in the bones as compared to the excreta. The ratio as it appears in the excreta may be estimated from two groups of periods during a constant low calcium diet, in which the excretion of *extra* calcium and radium must come from the bones. If one compares the metabolic periods 5 to 10 with periods 18 to 21, in this case, one finds an increased calcium of 0.43 gram and radium excretion of 4.7×10^{-9} gram per period. From our calcium analyses of bone (0.233 gram of calcium per gram of dried bone), 0.4 gram of calcium represents approximately 1.7 grams of bone, which would indicate that this patient had an approximate radium content of 2.8×10^{-9} gram per gram of bone.

The radium concentration in the bones of this case can be estimated in three other ways. (1) By actual analysis of two bone samples, which were necrotic trabeculae spontaneously extruded from her jaw, we found 196

and 13.6×10^{-9} gram of radium and 0.212 and 0.230 gram of calcium per gram of bone

TABLE III
Analyses of Dried Bone and Gall Stones

Patient	Area	Wt of Dried Bone analyzed	Calcium per gm of dried bone	Radium per gm of dried bone
No 2—E C	Spicules from gum	gm 0.301	gm 0.230	$\times 10^{-9}$ gm 13.6
	Spicules from gum	0.075	0.212	19.6
C I	Fibula—Trabeculae	0.403	0.200	1.75
	Fibula—Shaft	1.164	0.238	1.63
	Tibia—Trabeculae	1.172	0.239	0.86
	Tibia—Trabeculae	1.849	0.255	1.30
	Tibia—Shaft	2.620	0.246	1.06
	Tibia—Shaft	3.357	0.256	1.79
	Vertebrae	1.219	0.242	2.38
	Gall stones (Total wt app 3.7)	Wt of gall stones analyzed gm 1.834	Calcium per gm of gall stones gm 0.032	Radium per gm of gall stones $\times 10^{-9}$ gm 0.022

Calculating from this ratio, the actual increase in radium excretion during therapy is about one-fifth that which one would expect from the increase in calcium excretion. However, it has been shown that bone areas vary distinctly in their radium content and the mere fact that this bone was composed of trabeculae and had been killed justifies the assumption that it was relatively high in radium content. (2) The average radium in bone may be estimated, however, from the known radium stored in them. If one assumes the bones to be 16 per cent of the total body weight (53 kg), and, knowing the total radium stored (18×10^{-6} gram), one obtains the average figure of only 2.1×10^{-9} gram of radium per gram of bone. (3) The average bone radium may be calculated from comparison with another case, in whom total radium and actual bone analyses were obtained. In this case (C I), who had approximately $5 (\pm 1) \times 10^{-6}$ gram of radium in her body, the average analysis of five bone samples (table 3) gave 1.53×10^{-9} grams of radium and 239 gram of calcium per gram of bone. By correcting this ratio for the greater total radium storage of our patient 2 (E C) the average radium content of her bones would be 5.4×10^{-9} grams of radium per gram of bone. With calculations as crude as these, it appears that this figure roughly corresponds with the calculation of bone radium concentration obtained from the excreta and from calculation 2 above. These results, and similar calculations on patient 1, suggest that excreted and stored Ca/Ra ratio roughly correspond. The conclusions may, therefore, be drawn that the methods employed here are not more efficient in extracting radium than in extracting calcium from bone. It is more likely that they are both excreted in their relative proportion in the body—though possibly the calcium is slightly more easily mobilized.

Patient 3 (R L) was a physicist who had inhaled a very small quantity of radium only seven weeks before admission to the hospital. The radium storage when he started the metabolic studies represented only $0.6 (\pm 0.1) \times 10^{-6}$ gram of radium, yet this patient who had only about $\frac{1}{25}$ of the radium present in the other two patients was excreting radium at a much more rapid rate than were they. During the first period on metabolic regime, he excreted 1 per cent of his stored radium per day. This agrees with Schlundt's observations that the early excretion of radium is at a rapid rate in comparison to the excretion after several years.

TABLE IV
Patient 3, R L Total Radium in Body 0.6×10^{-6} gm
(Intake and Output in 3-day periods)

Period	Diet and Medication	Serum Calcium	Calcium Excretion		Radium Excretion						
			Urine	Feces	Urine	Feces					
Preliminary (4 weeks after accident)		mg %	gm	gm	$\times 10^{-9}$	gm 45.0					
First Admission to Metabolic Ward—7 weeks after accident											
1 2 3	High calcium diet	10.6			0.28 0.32 0.27	18.0 15.0 11.5					
	Low calcium diet (0.33 gm Ca)										
	Thyroid Extract	NH ₄ Cl					Parathyroid Extract				
	gr	gm					units				
	4	9					10.8	0.59	0.34	0.21	10.0
	5	12					11.6	0.69		0.22	10.0
6	12	11.9		0.24	10.0						
7	15	11.6		0.24	11.0						
8	3	15	11.9	1.24	0.36	0.23	12.0				
9	3	15	11.6	1.25	0.38	0.23	9.3				
10	3	15	11.6			0.22	12.7				
Second Admission—24 weeks after accident											
11 12	High calcium diet	10.6			0.05 0.05	1.5 1.2					

The rate of radium excretion was obviously falling very rapidly before medication was started, a decrease which one would expect to progressively

continue The medication which we were able to give this patient was never large in amount and could be increased only slowly because of his sensitive, nervous make-up The result of the medication was to raise his blood calcium approximately 1 milligram, but we did not produce an acidosis inasmuch as the CO_2 content of his blood at the end of treatment was 22.3 millimeters per liter (low normal equals 25 millimeters) and the pH of his blood at that time was 7.4*. We, therefore, must assume that the therapy that this patient received was only moderate, and the effect on his radium excretion was to prevent a further decrease and, in fact, to initiate a slight increase in excretion (table 4)

When one considers the very moderate effect on the *calcium* excretion produced by medication and the very low Ra:Ca ratio in the bones (because of the small amount of stored radium) one should expect that the increase in radium excretion would be negligible As a matter of fact, if the reasonable assumption is made that the continued fall of radium excretion seen in the control periods would be progressive, then the effect of therapy on the radium excretion is striking and of a far greater magnitude than that found in the chronic cases This is further brought out by the markedly reduced excretion found approximately three months later, when the total radium content of his body had fallen to so low a level that it could not be quantitatively measured from gamma ray observations

Alveolar Air and Blood Concentrations Samples of normally expired air were obtained from all three of the patients at various times The numerical results are given in table 5

All radium slowly disintegrates spontaneously into the radioactive gas, radon, which has a half-value period of 3.8 days It is noteworthy that in each of the cases studied about 45 per cent of the total radon produced by the decay of stored radium escapes continuously from the body through the lungs This fact indicates the intimate nature of the contact between the circulating blood and the stored radium (which is located almost exclusively in the bones) Specimens of approximately alveolar air were also collected and analyzed for radon The technic of these collections and analyses has been previously described¹⁶ Table 5 shows that the radon concentration in the alveolar air is about two or three times that of normal expired air As one would expect, there is no significant change in the breath radon values during the course of medication No therapy would affect the production of radon, and its blood concentration and excretion by lung would be dependent upon the various gas laws

It naturally becomes of interest to determine the radium content of the blood The radium analytical technics are sufficiently delicate to permit approximate analyses of 5 c.c. of blood, though somewhat erratic values of blood radium were obtained From a series of analyses, there seems to be slightly less radium in the red blood cells than in the serum The blood of patient 2 (E.C.) was repeatedly analyzed and showed a mean value of the

* We take this occasion to thank Professor Baird Hastings for these analyses

order of 1×10^{-12} gram of radium per cc of blood Assuming a total volume of 5 liters of blood this is 5×10^{-9} gram of radium in the blood, or only about 0.03 per cent of her total body radium (18 micrograms)

TABLE V
Measurement of Gamma Rays in Body and Radon in Breath

Patient	Period	Gamma Rays	Breath	
			Normal	Alveolar
No 1—M H		10^{-6} g Ra (as Ra C)	10^{-10} Curie/liter	10^{-10} Curie/liter
	2		1.66	
	6		1.71	
	9		1.34	
	11		1.67	
	One month after medication	8.5 (± 0.5)		
No 2—E C	1	10.0 (± 1)	1.9 (± 0.1)	
	3	9.7 (± 1)		
	9			3.6 (± 0.05)
	10		2.1 (± 0.05)	
	13		2.0 (± 0.1)	
	21		4.3 (± 0.1)	
	24	10.0 (± 1)	3.8 (± 0.2)	7.2 (± 0.1)
	38	11.0 (± 1)	2.6	7.7
No 3—R L	Preliminary	0.25 (± 0.1)		
	Preliminary	0.50 (± 0.1)		
	2	0.33 (± 0.05)		
	3		0.030	
	4		0.043	0.053
	5		0.044	0.055
	7			0.036
	7			0.066
	9			0.056
	12	0.15 (± 0.1)		0.034

Even knowledge of the approximate order of magnitude of the average radium concentration in the blood allows us to make several interesting calculations. Blood specimens taken from patient 2 (E. C.) during period 24 show an average of 0.95×10^{-12} gram of radium per cc of blood. This was a period of relatively low urinary radium output, but will serve for calculation. The kidneys eliminated 0.04×10^{-9} gram of radium per day during this period. As the blood supply to the kidneys is at least 500 liters per day,³² the blood stream carried an equivalent of $5 \times 10^5 \times 0.95 \times 10^{-12} = 5 \times 10^{-7}$ gram of radium, therefore, less than 0.01 per cent was removed continuously from the blood stream and eliminated from the body. Only about 1 per cent of the radium in the blood stream at any one time was removed per day. This computation emphasizes the relative ineffectiveness

of the kidneys in removing radium (and possibly other heavy metals) from the blood stream

During this period 24, the fecal elimination was 2.5×10^{-9} gram of radium per day, or 60 times the urinary elimination. Considering the vastly greater blood supply to the liver and gut we can say that the overall permeability of these organs to radium appears to be of the same rough order of magnitude as for the kidney. During period 18, the blood radium averaged 0.5×10^{-12} gram of radium per c.c., while the fecal elimination was 3.5×10^{-9} gram of radium per day. Here a similar calculation shows the daily elimination to be slightly greater than the total blood radium content at any moment of the day. These rough approximations suggest that it is less difficult to get radium out of the bone and into the blood stream than it is to get radium out of the blood stream and into the excreta.

DISCUSSION

From these observations, one may get a fairly clear-cut picture of what happens in radium poisoning. In the acute stage, during the first few months after exposure, the radium is scattered through the body and obviously more loosely held than later, and is therefore excreted at a far more rapid rate. In the later stages the bones hold onto the radium more tightly than at first. From the observations of Calhoun, et al.,²³ it is obvious that soon after heavy metals have been absorbed the trabeculae of bones have a relatively high concentration to that present in the cortex, while as time goes on there develops a more even distribution. Due to the relatively great amount of cortex, it is obvious that the greater proportion of radium is eventually stored in this part of bone. Inasmuch as it has been shown that the trabeculae are readily available for mobilization, and inasmuch as the radium is at first widely distributed in the organism, this gives a partial explanation of the relatively large liberation in the early weeks. As time goes on, it is to be expected that the cells should be injured or even killed in the area where radium is stored, and that the bones would respond less effectively to medication directed toward influencing their metabolism. In the patients we have studied, however, there has been a definite response to such medication, though in these chronic cases this has not been of a magnitude to greatly influence the total radium stored. Yet in spite of this relatively small percentage rise of radium excretion, a dramatic recovery from bone necrosis followed therapy in one of the patients (Patient 1 (M. H.)). Whether this was a matter of chance will remain a problem until further accumulation of evidence. It is obvious that such an improvement is only apt to occur when patients are treated relatively early before bone cells may be sufficiently injured so that recovery cannot take place. It remains for further studies to show whether this clinical improvement in this late case was due to a redistribution of radium in the bones, by largely dissolving trabeculae such as surround the teeth.

CONCLUSIONS

Radium stored in the body is analogous to lead in distribution, mode of excretion, and relationship to calcium metabolism

When radium is absorbed before the union of bone epiphyses, this area of bone may appear abnormal

Most stored radium (more than 90 per cent) is eliminated in the feces even when the excretion is artificially stimulated

The bile contains radium, and therefore also appears to be a route of excretion

Radium excretion can be elevated four to eight fold by decalcifying therapy, but this still does not greatly reduce the total stores of radium in the body

The response of radium excretion to deleading therapy is slower than is the calcium response. The excretion rate rises slowly and is prolonged after therapy has stopped. The probable mechanism involved is discussed

The administration of magnesium gluconate appears to elevate radium excretion just as it affects calcium excretion

One case of advanced, chronic radium poisoning gave no response to large amounts of parathyroid extract, possibly because of damage to bone cells. The only response to activated ergosterol was to maintain a high level of radium excretion. Nevertheless, storage of calcium was still accomplished when a high calcium diet was administered

The rate of increased radium and calcium excretion, after the effects of therapy have been established, indicates that the efficiency of treatment is roughly the same for both, and it is probable that the average Ca:Ra ratio present in bone is approximately similar to that of the stored metals excreted

CASE HISTORIES

Patient 1 (M. H.) was a woman of 54. About 10 years before entrance she was given an unknown amount of radium intravenously for arthritis. Neither the number of injections nor the amount of radium can be ascertained. There is also the possibility that she drank a little "radium water." Thirty-two months before entrance, she had a left lower molar tooth removed, and after this her jaw never healed and subsequently had to be repeatedly curetted. A year later the few remaining teeth were removed, and the entire left lower jaw was curetted. This continued not to heal, and spicules of bone continued to appear until eight months before entrance, when stored radium was found but was not quantitatively determined. At that time she had six weeks' treatment with low calcium diet and daily oral administration of six grams of ammonium chloride and two grains of Armour's thyroid extract. After this treatment she returned to a high calcium diet. The chronic area in her jaw promptly improved, but was still draining in November 1934, when she entered the hospital for further treatment.

Physical examination was essentially negative except for necrosis of her jaw. She remained in the hospital until December 15 on therapy outlined in her table then returned home and remained on a low calcium diet, but without further medication until she was readmitted to the hospital on January 16, 1935. She was then given a high calcium diet, and in addition 8 grams of calcium gluconate daily, and the last control observation was then made.

A roentgen-ray of the jaw on January 30, 1935, showed considerable filling in with new bone which had occurred within the last eight weeks. Since this time her jaw has progressively improved. The sinuses stopped draining within two months, and for the last year the bone has had a practically normal appearance.

All the laboratory results were normal except that the red blood count was 3,900,000, though the hemoglobin was 91 per cent (Sahli). The plasma phosphatase on entrance was 0.12 Kay units (average normal value 0.15), and 0.20 Kay units after therapy was discontinued.

Patient 2 (E. C.) was a 30-year-old woman, who entered the hospital complaining of painful feet on walking. Just 14 years ago, when she was 16 years old, this young lady began painting luminous numbers on watch dials, and since then she has been almost continuously employed in the same work. For the first seven years the brush was touched to the lips to point it for the delicate work. For the past seven years the painting has been done with glass pens, and under far better hygienic conditions. Five years ago, she began to notice aching in the right ankle when walking, and two years ago the right foot was put into a plaster jacket for one year. One and one-half years ago, the pain started in the left hip. Four years ago she first had trouble with her jaw. It became swollen and three teeth were subsequently pulled, and the upper jaw remained swollen for several months thereafter. It did not really subside for six months, with continuous drainage since that time in both upper and lower jaw. These sinuses have produced very little pain. Five months ago a tooth dropped out of the right upper jaw spontaneously. The patient's diet was adequate but she rarely drank milk. About six months before entrance, radium was first detected in her body.

Her physical examination appeared normal except the jaw which showed a small area of exposed bone in the right upper area, and also a loose piece of cancellous bone between teeth in the left upper jaw. There was a very small draining sinus in the left upper jaw.

Four days after her admission she lost a small piece of cancellous bone from the right jaw. The second piece, which was very loose on entrance, came away after a month in the hospital, and the third very small piece from the same area came away three weeks later. There did not seem to be any other loose bone about her teeth. The bone pains practically disappeared after she had been in the hospital several weeks, but before her discharge they returned in about the same intensity as on entrance.

Her stay in the hospital was without untoward incidence, except that on the forty-second day after admission she complained of right-sided abdominal pain, a little nausea, and loss of appetite. This was possibly a mild attack of appendicitis, but it promptly subsided without therapy. Her study was continued for 18 weeks, and she left the hospital in excellent condition.

Extensive laboratory studies were all negative save for an anemia of 3,600,000 with 63 per cent hemoglobin (Sahli) which developed while she was in the hospital. This was completely relieved within a month following iron and liver therapy. There were a surprising number of stippled cells seen in all of her blood smears, sometimes more than one in each field. The roentgen-rays of bones showed interesting small areas of rarefaction and eburnation scattered through the trabeculae. There was distinct pathological union of the epiphyses of shoulders and hips, indicating a definite radium influence before epiphyseal closure. The treatment and pertinent laboratory studies are shown in the table. Plasma phosphatase was consistently low throughout her stay in the hospital, being 0.06, 0.07, and 0.06 Kay units.

Patient 3 (R. L.) was a physicist (male), 54 years of age. Fifty-three days before entrance he was sealing a mixture of 100 milligrams radium chloride and 5 grams of beryllium powder into a steel tube when the plug was blown off this tube and some of the mixture filled the room. Some particles settled on his face. While still in the laboratory he washed himself carefully, but it is probable that he breathed

some of the dust at this time. He promptly thereafter had his eyes and teeth carefully cleaned. There have been no symptoms following this exposure to radium. The patient is well except that he had had indigestion for several years prior to five years ago, when an appendectomy was performed. Since then his digestion has improved.

Physical examination was not abnormal.

The patient was maintained on a high calcium diet for three periods, during which time he was allowed to eat what he pleased, except for a daily ration of one quart of milk. He was then put on a carefully weighed low calcium diet, and started at the same time on 3 grams of ammonium chloride a day. The subsequent medication is indicated on his table. Until his discharge 30 days after entrance, the patient continued on a very moderate amount of medication because he was afraid his old indigestion would be reprecipitated, and therefore only mild doses of medication could be used. Careful laboratory studies were all normal. He had no anemia, and his blood phosphatase determination was also normal, being 0.14 Kay units on entrance.

He then went to Europe for the summer, remaining on a rather low calcium diet. He had excellent health all summer and spent much of his time mountain climbing. After 12 weeks he returned to the hospital where he remained for seven days. During this period of observation his radium excretion was measured for control purposes, while he was given a full diet with added milk. It is interesting that he had gained 11 pounds in the 10 weeks between the two hospital admissions.

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GONORRHEAL ENDOCARDITIS WITH BILATERAL PAROTITIS AND TOXIC JAUNDICE AS ADDITIONAL COMPLICATIONS ⁺

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THE first case of gonorrheal endocarditis in which the gonococcus was grown by blood culture, as well as by cultures from thrombi on the heart valves, was reported by Drs. Thayer and Blumer¹ in 1896, in the Johns Hopkins Hospital Bulletin. Previously, there had been a few cases in which the organism found in endocarditis was morphologically and tinctorially characteristic of the gonococcus. It was also intracellular in the smear made at autopsy. Since then, cases presenting this complication in gonorrhea have multiplied, until in 1932 Hoffman and Taggart,² after a careful review of Thayer's list³ of reported cases, rejected six of them and added seven more, including one of their own, so that at that time 76 instances of this condition were found to have been reported. More recently, additional cases have been reported, for Eakin⁴ in 1934 found two more, increasing the number to 78, and in the years that have followed more have been published, so that now about 150 reputed cases have been recorded. In 1934, Stone,⁵ after a careful analysis of all of the reported cases, divided them into four groups totalling 123 cases. He allotted to the first, or proved group, 85 cases, to the second, or presumptive group, 12 cases, to the third, or probable group, 15 cases, and finally to the fourth, or possible group, 11 cases. In this list he could find only 34 cases in which the gonococcus had been grown by blood culture, although in 71 of the 112 cases falling within the first three groups, blood cultures had been made and in 14 of them, where the gonococcus had not been found by blood culture it had been grown from the heart's blood, vegetations, joint, pericardial or pleural fluid. Thirteen additional cases⁶ have yielded positive blood cultures in the years that have intervened since then. Of course some cases of this condition have existed, and do now exist, from whose blood culture the gonococcus has never been isolated, although numerous attempts have been made to grow it. On the other hand, the organism has been grown by blood culture in cases of bacteremia in which there has been no demonstrable cardiac involvement. Tabbutt,⁷ for example, has reported two such cases. Jenkins,⁸ O'Brien and Bancker,⁹ Wheeler and Cornell,¹⁰ Rubenstone and Israel,¹¹ Fillel,¹² and Friedberg¹³ also have reported similar cases with recovery. Others probably exist in the literature upon this subject. The

* Received for publication August 14, 1937

recoveries from this condition have been few, but they are not as rare as was formerly supposed. Stone¹⁴ lists six of them, and Newman¹⁵ adds nine to their number. Since then, two more have been reported. Kolle and Hetsch¹⁶ were of the opinion that only 0.7 per cent of all the patients who acquired gonorrhea developed gonococcal septicemia. The portal of entrance of the organism in every case is the genito-urinary tract, although occasionally the primary focus cannot be discovered. The history of our case is as follows:

CASE REPORT

Gonorrheal cervicitis two weeks following exposure, chills and evidence of cardiac involvement two months later followed in two weeks by recovery of the gonococcus by blood culture after five negative results, typical course of endocarditis with subsequent onset of bilateral parotitis and terminal toxic jaundice

S. V., female, aged 17, worker in the tobacco fields, was admitted to the Hartford Hospital on the Gynecological Service on August 23, 1934, complaining of pain in her right side. This symptom appeared 10 days before, but subsided quickly only to appear again the day of her entrance into the Hospital with nausea but not vomiting. She thinks she had some additional pain, however, at her June period, and may have had some fever on that occasion. Four months ago, about the middle of May, while returning with her partner from a dance, she was violently attacked by him and raped. Fourteen days subsequently a profuse yellowish vaginal discharge was noted. Her period, after the attack, came on two days later and continued for five days. Previously it had always been regular every 28 days, and of two to three days' duration. Now she is a few days over-due, and is much concerned about it, fearing pregnancy. She thinks that in the past month she has not felt as well as she normally does, and that occasionally she has had sensations of chilliness and fever. Her family history and past history were negative.

On admission she was found to be a well developed and well nourished woman, with face somewhat flushed, she was lying comfortably in bed and did not seem ill save for her flushed facial expression, the lungs were negative on examination, while the heart, though not enlarged and with sounds of normal relative intensity, showed at the base in the pulmonic area, a slight blowing systolic murmur. The abdomen was negative save for slight tenderness in the right lower quadrant. By vaginal examination the urethral orifice showed slight reddening with the presence of a slight, milky discharge, while from the vagina a profuse, yellowish discharge was noted. Bi-manual examination revealed slight tenderness in the right lateral fornix. Her temperature on admission was 101.2°, and her leukocyte count 25,200, with the polymorphonuclears 95 per cent and the mononuclears 5 per cent.

On August 27, Dr. Howe made the following note: "Nulliparous type of introitus, profuse thick flocculent discharge, Skene's ducts injected and a thin, milky discharge is readily expressed from them, smears taken. Cervix shows a slight degree of erosion about the external os, otherwise negative. Fundus normal in size and consistency, freely movable with some tenderness, no masses palpated, but patient is acutely tender on the right side. Impression: Acute skenitis, vaginitis, urethritis and endometritis probably Neisserian in origin. Treatment: Rest and expectant treatment." Twelve days later he noted the examination showed no change, save that the tenderness had disappeared but the local condition was unchanged in spite of the daily douches and routine treatment. A blood culture was taken on September 7, and I was asked to see her five days later.

Being on the Medical Service, I thought as her heart and lungs were normal that her pelvic condition might account for the temperature, and advised that she

remain at present on the Gynecological Service. I suggested further blood cultures, as well as a search for malarial organisms. The soft, systolic murmur which had existed at the pulmonic area since admission, did not appear to have any especial significance. Her temperature since admission had shown marked remissions, resembling closely a picket-fence. I advised at a second consultation on September 17, that a culture be taken at the height of her temperature, and again at its lowest point. A cystoscopic examination was performed the next day with negative results. On September 20 she developed marked systolic and diastolic murmurs at the base in the



FIG 1 Pulmonic valves with vegetations

pulmonic area. Convinced that the septic process was localizing itself on the pulmonic valve, although the blood cultures had been uniformly negative, I accepted her for transfer to my Medical Ward. In spite of five negative cultures, I ordered one of my interns to take another culture, plant it at the bedside and proceed at once with it to the Laboratory. We were shortly thereafter rewarded with the report of a gram-negative diplococcus being found, which was culturally and morphologically typical of *Neisseria gonorrhoeae*. In the culture from which it was isolated there were approximately 9 colonies per c c of blood. Some weeks later, on October 24, another successful blood culture was obtained with approximately 80 colonies per c c of blood. The patient was given twice weekly transfusions of 250 c c of blood, with no improvement (14 in all). The febrile excursions became less marked, but the chills, which were first noted on September 20, continued. After this first one, they were daily for three days, then after a five day interval, daily for seven days, and subsequently after one or several days interval continued daily until her death. A severe and intractable cystitis developed about October 15, which nothing seemed to

relieve About this time she complained of pain in the left upper quadrant, but the spleen was not palpable until November 9 Eleven days later a bilateral parotitis was observed, which quickly responded to cold applications The patient now became increasingly somnolent, was often irrational and was at times a difficult nursing problem The murmurs at the pulmonic area became much more pronounced, she developed a toxic jaundice with bile in her urine and died on November 28

Laboratory Data *Urine* August 24, 1934 Yellow, clear, no sediment, acid, specific gravity 1.010 Albumin, none, sugar, none, microscopically, a few white blood corpuscles A month later a few hyaline and granular casts were seen, the white blood corpuscles showed an increase and some red blood corpuscles were noted The white blood corpuscles soon became more numerous and showed distinct evidences of cystitis by their numbers, singly and in clumps The specific gravity varied from 1.009 to 1.025 Bile was found in the urine on November 25, 1934 The non-protein nitrogen on October 10 was 33 mg per cent but by November 21, it had risen to 70 mg per cent *Blood* The leukocyte count on entrance has been given By September 3, it had fallen to 9,100, while the differential count showed Polymorphonuclears 79 per cent, lymphocytes 19 per cent, mononuclears 2 per cent On September 14, the hemoglobin was 60 per cent and the red blood corpuscles 3,650,000 A week later the hemoglobin had fallen to 56 per cent, while the white blood count was 13,450, with the following differential count Polymorphonuclears 92 per cent, lymphocytes 6 per cent, mononuclears 2 per cent There was slight anisocytosis present In the next month, on October 16, there was not much change save in the white blood count which had risen to 19,200 The hemoglobin and red blood corpuscles showed slight change until the end, but the white blood count fell on November 10 to 10,900

Electrocardiograms Were made on September 26 and October 8 Dr Robert S Starr, our cardiologist, made the report on both of them The first showed a pulse rate of 105 per minute, with normal rhythm, P R interval 0.14 second Impression a normal E K G In the second, the only difference was in an increased pulse rate, it being 120 per minute

Cultures *Blood* Four blood cultures were taken on September 7, 13, 17, 19 and 21 with negative results Finally, one was taken on September 28 and brought quickly to the laboratory It showed a gram-negative diplococcus culturally and morphologically typical of *Neisseria gonorrhoeae*, with approximately nine colonies per c c of blood, while another on October 18, showed a similar organism in larger numbers, 80 colonies being seen approximately per c c of blood

Urine The urine showed on September 17 the *Staphylococcus pyogenes aureus*, the *Streptococcus hemolyticus* and non-hemolyticus and the *B. fecalis alkaligenes*, but on October 19, only the *Staphylococcus pyogenes aureus* and the *Streptococcus non-hemolyticus* were grown Five smears from the cervix and urethra were taken and were negative for gonococci

An autopsy was performed by Dr Perry Hough two hours after death The anatomical diagnosis was *gonorrheal cervicitis, gonococcus septicemia, acute pulmonary gonococcus vegetative endocarditis, acute splenic tumor, chronic passive congestion of the kidneys and jaundice*

There was a marked icterus of the skin and conjunctivae, besides small, irregular petechiae which were scattered profusely in the skin over the upper and lower extremities The changes in the lungs, heart, spleen and kidneys merit full description, and were as follows

Lungs Right 350 gm Left 300 gm There are no adhesions and no appreciable amount of fluid in the pleural cavity On section there is practically no edema or congestion Scattered throughout both lungs, especially in the lower lobe, there are a few dark, nodular areas, appearing to be small areas of infarction, and in the base of the right lower lobe there is one wedge shaped area of infarction just outside of the

periphery about $1\frac{1}{2}$ cm in diameter. There is no pneumonic consolidation. The bronchi and peribronchial lymph nodes appear normal.

Heart 240 gm. There are about 80 c.c. of cloudy, amber fluid within the pericardial cavity. The right ventricular wall is 4 mm in thickness, the left ventricular wall is 15 mm, and there is a marked dilatation of the right side of the heart with less dilatation of the left. The myocardium everywhere appears grossly normal. The aortic, mitral and tricuspid valves are grossly normal. The leaflets are thin, and pellucid, with no vegetations. The pulmonic valve is markedly involved with large, varicose, buff-colored, friable vegetations extending completely around the ring, involving all of the leaflets. The largest averages 2 cm in diameter and is attached by a broad pedicle. There are smaller, nodular, similar vegetations extending for about 2 cm along the pulmonary artery and scattered diffusely over the endocardial surface of the right ventricle in the region of the pulmonic valve. The coronary arteries are thin and patent throughout.

Spleen Tremendously enlarged, weighing 1100 gm and extending 9 to 10 cm below the left costal margin. Splenic notch is preserved. On section the organ is moderately firm and dark red in color. The malpighian corpuscles are rather indistinct and at one point toward the lower pole there is a small, somewhat lighter area than the surrounding tissue of slightly increased density, possibly representing a small infarct. It covers a diameter of approximately 1 cm.

Kidneys Weight together, 420 gm. Capsule thin, and strips easily, leaving a smooth cortical surface over which there is scattered diffusely tiny areas of hemorrhage, averaging less than 1 mm in diameter. On section the cortex is swollen. Tiny hemorrhages are seen throughout the cortical tissue and the normal striations are somewhat indistinct. Renal pelves and ureters are grossly normal, as is the bladder.

Genitalia Negative, save for a few tiny cysts in the upper and posterior cul-de-sac of the vagina, averaging 1 mm in diameter. The tissue is here moderately indurated.

Microscopic Examination

Lungs Microscopically normal except for the areas of infarction mentioned in the gross. These microscopically appear to be typical infarcts with degeneration of the alveolar walls, the alveolar spaces being engorged with blood cells, serum and old blood pigment. In one section, apparently from one of the old infarcts, there is complete necrosis. Around the margin there are a few polymorphonuclear leukocytes, and interspersed among these there is a suggestion of bacteria having a coccus form but not being definitely biscuit-shaped diplococci.

Heart Section of the heart valve shows superimposed upon it a vegetation consisting of well organized thrombus in which many proliferating fibroblasts are seen along with a few polymorphonuclear leukocytes and a moderate small round cell infiltration. Special stain reveals through the vegetation colonies and isolated groups of gram-negative diplococci microscopically typical of gonococci.

Liver Essentially negative.

Spleen Splenic sinuses are engorged with red blood cells and throughout there is an accumulation of brown pigment, apparently old blood pigment. There is no increase in the reticulum elements. The malpighian corpuscles are rather small and somewhat distorted. No areas of infarction are seen microscopically.

Kidneys The tiny hemorrhages mentioned in the gross appear microscopically to be only dilated capillaries engorged with red blood cells and old red blood pigment. There is no actual hemorrhagic extravasation in the renal parenchyma. There is cloudy swelling of the tubular epithelium. The glomeruli everywhere appear normal. No interstitial fibrosis or red cell infiltration. A few tubules, however, contain casts composed chiefly of degenerated blood. No gonococci found by postmortem culture.

Genitalia No evidence of acute inflammatory reaction in the sections from the

vagina The epithelium in one portion has been denuded apparently at the site of one of the small cysts mentioned in the gross Underlying the epithelium there is a slight infiltration with small, round cells Cervix Presents a similar picture The epithelium is everywhere intact, but beneath this there is a definite layer of chronic inflammatory reaction, consisting essentially of small round cells with a slight degree of fibrosis Salpinx Negative

SUMMARY AND COMMENT

Our patient was a woman, aged 17 years, who developed an acute cervicitis two weeks after the exposure to infection, an endocarditis followed after an indefinite period, followed in turn by a bi-lateral parotitis and a terminal toxic jaundice The blood culture was positive and the pulmonary valve was found to be involved at autopsy Since this case was seen, two other methods for the treatment of gonorrhea have been utilized, namely artificial fever¹⁷ and the drug sulphanilamide Both seem to offer something in the way of treatment

Dr W S Thayer¹⁸ has shown that the aortic valve is most commonly implicated in this disease, and that the pulmonary valve is more commonly affected in this variety of endocarditis than in the sub-acute type Although gonorrheal endocarditis generally follows an arthritis, a study of this case shows that this latter complication was absent An initial chill probably ushered in the heart involvement The bilateral parotitis which occurred later in the disease, was probably due to bacteria which were secondary invaders Jaundice is a rather unusual development and probably had a toxic etiology It was seen in Silvestrini's case¹⁹ which recovered, and in Blumer and Nesbit's fatal case²⁰ where it was associated with a hepatitis

Recently Lichtman²¹ has reported a case in the *Journal* of the Mt Sinai Hospital in which he considers that the jaundice probably resulted from rapid and extensive blood destruction, overactivity of the reticulo-endothelial system and liver cell damage due to bacterial toxins The presence of bilirubin in the urine indicates a regurgitative type of jaundice associated with hepato-cellular necrosis Lichtman refers to a former article he wrote in conjunction with Kugel²² on "Factors Causing Clinical Jaundice in Heart Disease" He also gives a reference to Popper and Wiedman's interesting article²³ on "Gonotoxic Icterus" In our case, the jaundice appears to be due to the effect of the gonotoxin on the parenchyma of the liver The red blood corpuscles remained about stationary at 3,500,000 Popper and Wiedman consider the jaundice caused by this microorganism generally similar to the simple catarrhal type, although occasionally cases are found resulting finally in acute yellow atrophy of the liver

The difficulty of cultivating gonococci has caused the number of these cases reported to be comparatively few in their relation to the total published number of cases presenting this complication A positive ante- or post-mortem culture is, however, the only absolute criterion for a diagnosis A

history of gonorrhea followed by a mono-articular arthritis which is in turn followed by an endocarditis offers strong presumptive evidence of the endocarditis being gonorrheal in origin. Indeed it would do so even if a mono-articular arthritis had not existed and even though the blood cultures were negative.

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THE NON-OPERATIVE TREATMENT OF HYPERTHYROIDISM *

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EVEN though, in the present day treatment of hyperthyroidism, operation is more frequently resorted to than is conservative treatment, nevertheless the latter still has a wide field of usefulness which is well worth reviewing. In Germany, opinion is still very much divided concerning the value of non-operative treatment. There are clinics where patients are seldom brought to operation and others which use only operative treatment. The majority probably occupy a middle ground. In this connection, I may refer to the questionnaire which we presented to several clinics a year ago.¹

A great many misunderstandings have arisen because of the fact that nomenclature is not uniform. Many authors distinguish special forms of the disease, which are, for example, termed "hyperthyroidism" as opposed to "complete Basedow." In America the toxic adenoma plays a special rôle which finds little or no recognition in Germany. It is particularly difficult to define the very mild cases, the transitions between "vegetative stigmatization" to "mild Basedow" or "Basedowoid," etc. In the presence of such confusion, statistics concerning the results of treatment by various authors can hardly be compared. The best conclusions can be drawn if, in the same clinic, some patients are referred for operation and a similar number are reserved for conservative treatment, after which the end results may be compared. My personal experience has such a basis.

We do not deny the possibility that there may be certain special forms of the disease—for example, those of pituitary origin or where the underlying cause is perhaps not an excessive amount of thyroxin, but another unknown toxic substance. The actual proof of the existence of such special forms is, however, not assured. It seems likely to me that in the majority of cases there are no qualitative differences, but only quantitative ones which are of significance. If the illness is frequently variable in form, we need not assume variable noxae, but simply that the same noxa results in different reactions in individuals of different makeups. This is also true in other diseases. In any case, it seems to me entirely satisfactory in everyday practice to speak of mild, moderate and severe forms. Here, the clinical picture, as a whole, must be the deciding factor. Of all the symptoms, the increase in the basal metabolism is probably still the best measuring stick, but it would be unwise to let this be the sole criterion. Cardiac disturbances

* Received for publication August 21, 1937
Translation by Robert W. Buck, M.D.

may be of much greater significance. The various symptoms are different, too, in different communities. In Berlin, for example, we see quite a number of patients who have no exophthalmos and little or no enlargement of the thyroid gland, so that the diagnosis is often not made.

One of the first needs which must be met is *psychic treatment*, although I question whether excitement or fright plays such a decisive rôle in the origin of hyperthyroidism as is often assumed. Nevertheless, it is certain that they are very significant in the further progression of the disease. Removal of the patient from the cares of daily life or freeing him from oppressive psychic conflict—for example, by conversation with a good physician—may cause apparent improvement. In this sense, a change in environment often has a good effect, as we see when the patients are brought to a hospital from a sanatorium. Perhaps, in this connection, certain *climatic factors* may be of significance, regions of moderately high elevation being favored. At any rate, certain sanatoria enjoy an especially good reputation, not entirely without reason, and specialize to a certain extent in the treatment of hyperthyroidism. *Physical rest* shares with mental reassurance the task of conserving calories, thereby combating emaciation in the presence of the elevated metabolism. On this account, a great deal of time in bed or even strict bed rest is indicated, at least for a few weeks.

For the same reason, the diet must be rich in calories, disregarding the unusual cases of obese patients with hyperthyroidism. Most physicians prefer a diet poor in protein on the ground that protein elevates the basal metabolism because of its specific dynamic effect. I do not think we need worry too much about this. At any rate, our first concern must be the maintenance and stimulation of the appetite by giving a mixed diet which should be rich in vitamins as well. There are certain definite indications for the administration of vitamin. For example, vitamin "A" is supposed to have a definite effect against hyperthyroidism. Wendt² has reported improvement with large doses, I, myself, have not as yet been able to arrive at any definite conclusion in this respect. However, this subject is still open.

Not a few patients have a tendency to *diarrhea*. This is in part the expression of a nervous acceleration of intestinal peristalsis and in part the result of a hypoacidity or anacidity of the gastric juice which is fairly common in hyperthyroidism. In every case of diarrhea, a fractional gastric analysis should be made because, in these cases, very definite improvement may be achieved by a rather careful diet, together with the administration of hydrochloric acid (e.g., acid hydrochloric non-dilut, pepsin sicc, 40.0, aquae q.s. ad 200), 1 teaspoonful in a glass of water, $\frac{1}{3}$ of which is to be taken through a glass tube before, during and after the meal.

Insulin and glucose are often prescribed, since in animal experiments a definite antagonism between thyroxin and insulin has been demonstrated. The general effect, however, is only slight. Nevertheless, in the presence of marked emaciation and loss of appetite, a trial is justified. Increase in weight is, to be sure, for the most part attributable to water retention.

Physical and mental rest may be effectively supported by means of *medication*. We give either bromides or, better still, drugs of the barbituric acid series. Luminal has, in general, proved most satisfactory. The dosage, however, must be strictly adjusted to the individual's peculiarities—in many cases, very small doses suffice, perhaps 0.015 gram two or three times daily. Other patients require much more, perhaps as much as 0.05 gram morning and noon, together with 0.1 gram in the evening. If luminal results in drowsiness rather than sedation, prominal should be tried, which has a predominantly sedative effect, approximately double the above dosage may be given. A favorite old-fashioned remedy to improve the general condition is arsenic in practically any form.

A great many of the symptoms of hyperthyroidism rest upon an irritability of the sympathetic nervous system. *Ergotamine* may be regarded as a direct antidote which lowers the excitability of this system. As a matter of fact, many symptoms can be markedly influenced with this drug—those such as tachycardia, tremor and even exophthalmos. However, if sufficiently high doses are given over a prolonged period, the danger of ergotism and gangrene of the extremities is considerable. Further, ergotamine often causes nausea. As a result, I have quite given up its use.

Repeated attempts have been made to discover anti-substances in animal blood which will be effective against the action of thyroxin. In this group belong the old antithyreoidin of Moebius, derived from thyroidectomized sheep, or Blum's thyronorman. Although these investigations are very interesting—in animal experiments the substances seem to be quite effective—nevertheless, in my personal experience I have seen no important practical results. It is possible, however, that further progress may be made along these lines.

Much more effective than the above mentioned methods is *iodine treatment*. Although the pre-operative administration of iodine over short periods of time, as introduced by Plummer and Boothby in 1924, is now recognized throughout the whole world, the prolonged treatment, as advocated in 1920 by Neisser in Stettin, is still disputed. However, our experience during the last few years has also brought a good deal of enlightenment in this connection. This much is certain: treatment with iodine is an art demanding intuition and experience, without these, harm may result. However, in the hands of an experienced man who knows the limitations of the treatment, it is extraordinarily effective. As yet we know very little theoretically as to what happens when iodine is administered and on this account we have had to depend all the more on our experience. This shows us the following facts:

The optimal dose lies between 50 and 200 milligrams of iodine daily, within these limits, individual variations can and should be made. Nothing is to be gained by giving larger amounts. Indeed, a single larger dose may occasionally lead to acute exacerbation of symptoms. The manner of ad-

ministration of iodine is unimportant, only the amount of iodine given being significant, whether or not the iodine is given in organic or inorganic form. Thus, we have seen no difference between calcium iodide, sodium iodide, Lugol's solution, di-iodide thyrosin or sajodin, so long as the above mentioned dosage of iodine was maintained^{3,4}. Frequently, however, by changing the form of the preparations, some of the unpleasant by-effects, such as iodine coryza or iodine acne, may be controlled, however, these by-effects are rare and often must be accepted as part of the bargain.

The favorable effect of iodine occurs after two or three days, reaching its maximum in one or two weeks, the basal metabolism falls sharply, the pulse rate becomes slower and, not infrequently, a completely irregular pulse becomes regular again, tremor grows less, exophthalmos often diminishes, the restlessness disappears and there is a gain in body weight. The great question is only—for how long a period does this improvement persist? The surgeons believe that operation should be performed at the maximum point of this improvement, which is, no doubt, correct in the majority of cases, if operation is to be done in any case. If operation is not performed, however, and iodine is nevertheless continued, the favorable effect gradually diminishes, at least, there is no further continuation in the improvement. It is well to stop treatment from time to time—for example, to give iodine for eight to 14 days and then to stop it for three to five days and to constantly repeat this series. This may be continued over several months. I wish to say very definitely, however, that a complete cure is almost never attained by these methods. As soon as iodine is given up for a prolonged period of time, the old symptoms return, sometimes, indeed, more marked than before. Here lies the danger in iodine treatment. If we once begin to use iodine, we do not dare to stop it unless an improvement is obtained in some other fashion—i.e., either by operation or roentgen-radiation. Further, after a course of iodine of long duration, particularly if intervals of freedom have been observed, one can still operate. In this way, very sick patients may show a marked gain of weight in the course of a few weeks and may be operated upon while in much better general condition. Of particular significance is iodine treatment of long duration in association with roentgen-radiation, which will be discussed below. The good effect of radiation begins only after a number of weeks. During this period patients can be maintained temporarily in very good fashion by means of iodine, which may be given up when the roentgen-ray effect is apparent. This seems to me to be the principal value of long-continued iodine treatment.

There are only a few patients who do not respond to iodine and in practice a trial of its use can be made in the most widely different forms of hyperthyroidism. It has an especially favorable effect in those cases of hyperthyroidism which have been induced by iodine. Even these cases do not, as a rule, occur during the period that iodine is being given (as, for example, in anti-luetic treatment or in arteriosclerosis), but rather more especially

when the iodine is discontinued. It requires some courage to give iodine again if it is known that the condition was caused by giving iodine. But experience shows that we must have this courage and that the patients become much better if we give them iodine again. Then, by all means, however, cure must be effected by operation or radiation.

It is also very important to give iodine if a patient with hyperthyroidism is attacked by an infection or meets with an accident. In this way he can be carried through a dangerous period.

Roentgen-ray treatment is also the subject of controversy. Here, however, the limits of treatment and its indications are gradually becoming clear.^{*} If a good roentgen therapist conducts the treatments, it is certainly even less dangerous than operation. Indeed, if radiation, as described above, is combined with intermittent iodine treatment, there is practically no mortality whatever to be considered. This is a great advantage which decisively determines the course of action for many patients and physicians. There are, however, very serious objections to this procedure. The number of complete cures is not nearly as large as with operation. If many authors, however, still deny that any good results follow roentgen-ray treatments, this can only be the result of insufficient experience or unsatisfactory technic. I am familiar with a whole series of severe cases which were completely cured after radiation, but, as a matter of fact, many complete failures also occur and one sees particularly often marked improvement, but no such complete cures as usually occur after operation. After a few months there may be recurrences. Often we can obtain further improvement after a new series of radiations, but the end result still remains less certain. A further objection is the long duration. As a rule, several weeks or often as much as three to five months elapse before the definite improvement begins. During this time very dangerous spontaneous exacerbation of the disease may occur and this is the principal reason why we demand simultaneous iodine treatment as above mentioned.

If no permanent results occur following radiation, not much time or money has been lost. It is possible, in spite of a widespread opinion, even then to operate without any special difficulty, if one has not waited too long. At any rate, I have seen a great number of patients who were operated upon several months after a course of radiation which was without result, and who were then cured.

The symptomatic treatment of *disturbances of circulation* demands

* My personal experiences are based upon patients in my ward, the iodine treatment of whom I have supervised and whose roentgen-ray treatment was undertaken in the wards of Dr. Muehlmann of Stettin and Prof. Frik of Berlin. As a rule, 10 roentgen-ray treatments were given with intervals between them of 8 to 10 days. After the fifth radiation, there was usually a rest of five weeks and the remaining five treatments were then given similarly to the ambulatory patients. A radiation of 185 roentgens, measured in air, 0.7 Cu half value layer over a large field including thyroid and thymus is given at a distance of 30 to 40 cm at each treatment so that in a period of ten to twelve weeks a total of approximately 1650 roentgens measured in air are given. The effective dosage in this area is not uniform but may probably be considered to be in the neighborhood of 1000 to 1100 roentgens measured in air.

special attention The simple tachycardia of hyperthyroidism, with its markedly short contractions of the heart, and *pulsus celer* is doubtless an unfavorable form of cardiac activity While in other cardiac conditions, digitalis slows the rapid pulse, here, for the most part, there is no clear-cut effect Only when definite circulatory failure with congestion of the liver and edema occur is it desirable to make use of digitalis As a rule, iodine, alone or in combination with digitalis, works much better Auricular fibrillation in hyperthyroidism is especially noteworthy It may be the expression of severe damage to the heart muscle, but frequently is only a transient symptom which is relatively easy to control in contrast to the auricular fibrillation caused by arteriosclerosis Auricular fibrillation occurs during periods of aggravation of the hyperthyroidism, as for example, during the first few days after thyroidectomy, and during periods of transitory improvement it may suddenly disappear Quite often the cardiac action becomes completely regular under iodine treatment, but as soon as iodine is omitted, the auricular fibrillation recurs The irregularity may also, for the most part, be corrected by means of quinidine or quinine, but, as is well known, the use of these drugs is not entirely without danger and should only be carried out by experienced persons with constant clinical observation

If, then, we search for indications for the various forms of treatment, we shall perhaps take the following position Very mild cases should perhaps not be treated at all, particularly not with iodine—they should be only watched These are the patients who have single mild symptoms, such as tachycardia, or vasomotor excitability with a tendency to profuse sweating, or a slight stare, etc Such cases have been designated vegetative neuroses or Basedow types No true disease is present, but they are on the borderline of normal For the most part, no true hyperthyroidism eventuates These people rather preserve their individual peculiarities throughout their lives

In the moderately severe cases, one has a choice between operation with a short period of pre-operative preparation with iodine and roentgen-ray treatment with prolonged iodine administration Operation is followed by a more rapid and certain effect Radiation is less dangerous, its effect is definitely slower and not so certain Therefore, one may decide in accordance with the courage and economic circumstances of the individual We strongly advise operation only in acute hyperthyroidism of only a few weeks or months duration, since the outlook here is especially favorable In older and more severe cases, we are inclined, on the other hand, to try radiation first Then, if operation is here resorted to, it is often desirable to give iodine not only during the short pre-operative period, but also intermittently over a longer period of time, together with all other symptomatic measures that can be used in order to improve the general condition

If, however, conservative treatment results in no cure after a few months, we unconditionally advise operation Temporizing in a half-cured

case of hyperthyroidism always carries with it the danger of the occurrence of thyrotoxic crises

These crises may arise at any time, their cause being unknown, often they are inaugurated by infection, particularly by pneumonia, to which these hyperthyroid patients are apparently particularly susceptible. A sudden increase in the pulse rate occurs, marked excitation, high fever and general collapse. When this stage has been reached, operation is of no avail. It would be foolish to consider radiation. Many times the patient may be brought out of the crisis by means of iodine, but, for the most part, it ends fatally.

SUMMARY

A review of the non-operative treatment of hyperthyroidism is presented—physical, psychic, dietetic treatment and especially the effect of iodine and roentgen-radiation. Their limits and indications are discussed.

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THE DIGESTIVE AND ABSORPTIVE FUNCTION OF THE EXTERNAL SECRETION OF THE PANCREAS

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THERE are some types of investigations which require many years of work before any considerable progress is made, studies of the digestive function of the external secretion of the pancreas are of such a nature. The difficulty in preparing suitable experimental conditions in animals, the care needed in controlling the many variable factors of each experiment, and the lengthy chemical analyses, require in some instances as long as a year to study a single case. J. H. Pratt has since 1907 almost continuously studied some aspect of this branch of physiology, and in recent years has actively directed the work of younger men including Hjort, Falcon-Lesses, Herschenson, Rosenblum, Krakower, Golden, Handelsman, Magendantz and others. The number of publications has been few because of the reasons mentioned, but a vast amount of unpublished data has been collected over the years. Some of these studies will be mentioned here.

In general, studies concerning the effect of excluding pancreatic juice from the intestine have given conflicting results. We have had cycles of beliefs varying from the idea that digestion and absorption of fat and nitrogen may be normal, to the belief that no fat and little protein is utilized in the absence of pancreatic juice. A historical survey shows that these conflicts date from early times.

HISTORICAL

As far back as 1682, Conrad L. Brunner¹ removed a large portion of the pancreas of dogs and claimed that the health and digestion of the animals were unaffected. It was Claude Bernard² in 1856 who showed that shutting off the pancreatic juice by injecting oil into the ducts caused serious disturbances in the absorption of fat.

Practically all the workers after Bernard were unable to confirm his observations. Frerichs³ in 1858 tried to destroy the pancreas by numerous ligatures and fed the animals with fat diets, at postmortem examination the lacteals were found more or less filled with white chyle. Herbst⁴ in 1853 had the same results. Weinmann⁵ in 1853 created pancreatic fistulae in dogs and fed them food rich in fats, he found no fat in the stools. Berard and Colin⁶ extirpated the pancreas in five dogs and left only that

* Received for publication July 20, 1937.

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portion lying next to the portal fissure. The animals lived eight months showing no digestive changes. Bidder and Schmidt⁷ in Germany also doubted the results of Bernard. Schiff⁸ in 1862 injected paraffin into the main excretory duct in dogs and found that fat digestion went on normally. Martinotti⁹ in 1882 asserted that after complete extirpation of the pancreas, no disturbances resulted either in the general condition or in the digestive functions.

The monumental work of von Mering and Minkowski¹⁰ in 1889 in Naunyn's Clinic which cleared up the relation of the pancreas to sugar metabolism, overshadowed the studies in the same clinic regarding the digestive function of the pancreas which were delegated to Abelman¹¹ (1890), then a student. Abelman showed that the removal of the pancreas is followed by enormous losses of fat and nitrogen in the stools. When given in the form of meat or lard, almost all the ingested fat was recovered in the stools whereas when the fat was in the form of a natural emulsion, namely as milk, only about one-half was found in the feces. With partial depancreatization, a larger amount was absorbed. De Dominicis¹² reached the same conclusion. Sandmeyer¹³ (1895) reported a partially depancreatized dog whose stools showed a greater amount of fat than had been fed.

That the presence of the pancreas in the body was necessary for digestion and absorption was then generally conceded, but that this action was due to the external secretion of the pancreas was denied. Lombroso¹⁴ (1894) found no disturbance in fat absorption when the pancreatic ducts were tied. Rosenberg¹⁵ (1898) found that in dogs where the pancreas had been separated from the intestine, there was only slight diminution in the absorption of nitrogen, and the fat absorption after having been normal for two months post-operatively was also very slightly diminished. Zunz and Mayer¹⁶ (1906) as well saw no digestive changes. Lombroso¹⁷ (1906) again repeated his earlier work and confirmed his former findings. Burkhardt¹⁸ (1908) obtained results contrary to the results of the above workers. He found the absorption of foods to be diminished when the external secretion of the pancreas was not allowed to enter the intestine—but when the same dog was allowed to lick the secretion from a pancreatic fistula good absorption occurred. To clear up the dispute, Lombroso¹⁹ (1908) went to Greifswald where Burkhardt¹⁸ had done his work, repeated the experiments in the same laboratory in Minkowski's clinic and apparently demonstrated that with the pancreatic juice excluded completely, absorption was good. Fleckseder²⁰ (1908), Niemann²¹ (1909) and Brugsch²² (1909) were also unanimous in their conviction that normal digestion and absorption could take place when the pancreatic ducts were tied and no secretion entered the intestine. This latter view was generally accepted and was incorporated by Adolph Schmidt²³ (1906) in Von Noorden's "Pathologie des Stoffwechsels."

Many of the above experiments were of dubious value, because the

stools were collected over one day periods which has been shown to be unreliable. However, to explain the above contradictions, three different theories were offered. First Lombroso¹⁹ postulated a pancreatic internal secretion which by its absence did not allow absorption of food when the pancreas was extirpated, but allowed normal absorption even when the pancreatic juice was excluded from the intestinal canal. Secondly, Abelman¹¹ (1890), Rosenberg¹⁵ (1898) and Burkhardt¹⁸ (1908) believed that when the pancreatic ducts were ligated, the digestive ferments enter the blood stream and then are secondarily secreted by other digestive glands, thus entering the intestine by other routes.

The third explanation was that most of the earlier workers had actually failed to exclude the pancreatic juice from the duodenum, and that this accounted for the excellent absorption reported in the absence of pancreatic juice. Hess²⁴ (1907, 1908) after careful anatomical and pathological studies found that there were in many cases three and sometimes four pancreatic ducts in dogs, and that in eight experiments he succeeded only twice in ligating all the ducts. In one of these two instances, only 4.73 per cent of the ingested fat and 54.68 per cent of the nitrogen was absorbed. The other instance showed 48.4 per cent of the fat and 42 per cent of the nitrogen was utilized. This latter result must be accepted with reserve because the dog had double empyema and enteritis. Sinn²⁵ (1907) corroborated Hess' anatomical studies. Pratt, Lamson and Marks²⁶ (1909) further pointed out that even after all the ducts are tied, sinuses may form through the necrotic tissue with the result that pancreatic juice again enters the intestine.

MORE RECENT EXPERIMENTAL EVIDENCE OF THE RÔLE OF THE PANCREATIC EXTERNAL SECRETION IN DIGESTION AND ABSORPTION

It was these investigators, Pratt, Lamson and Marks²⁶ (1909), who first conclusively demonstrated that the confusion of results was due to most of the workers' failure to exclude pancreatic juice from the intestine. Four out of five dogs were successfully operated upon and proved at autopsy to have had all their pancreatic ducts completely ligated so that none of the digestive ferments could have entered the intestine. These animals showed a markedly diminished absorption of fat and nitrogen as evidenced by the enormous quantities found in the stools both by clinical tests and careful chemical analyses. Similar metabolism and absorption experiments on three additional dogs by Francis G. Benedict and Pratt²⁷ (1913) yielded the same results. Vinsentini²⁸ (1914) brought forth more experimental evidence in five dogs with completely ligated ducts also showing that there was a marked decrease in fat utilization. Brugsch²⁹ (1919) published a report of work done from 1912 to 1915. He was able to ligate the pancreatic ducts and to exclude completely the pancreatic juice in only three out of eight attempts. Those animals successfully operated upon showed a marked diminution of nitrogen and fat absorption leading Brugsch to change his former views and to agree with Pratt.

It must be pointed out in this connection that despite the above experimental results Lombroso³⁰ (1931) again reaffirmed his beliefs that an internal secretion of the pancreas controls fat absorption. Umber³¹ (1926) and Lesser³² (1925) writing in recent German "Handbucher" still put considerable credence in Lombroso's theory. However, McClure, Vincent and Pratt³³ (1917) showed by direct experimentation that "the absorption of food was no less when the pancreas of a dog was entirely removed from the body than when the pancreas was left in the body but its secretion excluded from the intestines." Vinsentini²⁸ (1914) obtained only slightly better absorption of fats in dogs with the pancreatic ducts ligated than in those from which the pancreas had been removed. Licht and Wagner³⁴ (1927) and Falcon-Lesses and Herschenson³⁵ (1931) conclusively demonstrated that the absorption of foods was the same in dogs in which first only the pancreatic secretion was blocked and then later the pancreatic remainder removed. These studies would tend to discredit completely Lombroso's theory of an internal secretion.

TABLE I

Results obtained by various workers regarding the percentage of dietary nitrogen and fat absorbed in dogs when the external secretion of the pancreas was unquestionably excluded from the intestines

Author	% Nitrogen Absorbed	% Fat Absorbed
Pratt (1907)—ducts ligated	22.2-61.7	4.8-76.6
Vinsentini (1914)—ducts ligated	—	28.7-44.0
Vinsentini (1914)—after pancreatectomy	—	8.7-25.7
Cruikshank (1915)—one stage pancreatectomy	78	32.6
Cruikshank (1915)—two stage pancreatectomy	79.6	72.12
Brugsch (1919)—ducts ligated	21.8-33.5	0-21.8
Licht and Wagner (1927)—ducts ligated and after pancreatectomy	55	0
Pratt, Falcon-Lesses and Herschenson (1931)—ducts ligated	85.3	93.6
Pratt, Falcon-Lesses and Herschenson after pancreatectomy	56.2	95.2
Pratt (1934) with Handelsman and Golden—ducts ligated	47-60	41.5-93.7
Selle (1937)—after pancreatectomy	—	average 89.51
Greenberg (1933) in cats—ducts ligated	51.2-66.8	0-28

Greenberg (1933)⁹¹ employing cats obtained results similar to those of Brugsch and Licht and Wagner. He also obtained more fat excreted in the stools than fed.

Although it is now agreed by most experimenters that the exclusion of the external secretion of the pancreas interferes with the digestion and absorption of fats and proteins, there still is tremendous difference of opinion as to how great a rôle it is that the pancreas actually plays. Particularly regarding fat absorption has there been great disagreement, some workers reporting no absorption and others obtaining normal values. We have tabulated the results obtained by various workers in table 1.

It can be seen that Brugsch²⁹ (1919) and Licht and Wagner³⁴ (1927) report no fat at all absorbed while Falcon-Lesses and Herschenson³⁵ (1931)

obtained almost normal absorption. It must be pointed out, however, that Licht and Wagner give no experimental data and a perusal of Brugsch's report reveals that he did not analyze his diets but based his calculations on the amount of solid fat added to the food. If the lipid content of the meat fed were also taken into account, the percentage of fat absorption in Brugsch's animals would probably be greater.

Cruikshank³⁶ (1915) first pointed out the importance of the general well being of the animal when absorptive studies are made. Working in Starling's laboratory he showed that a dog which had been carefully depancreatized in a two stage operation absorbed a large percentage of fat, whereas a dog which had been completely depancreatized in one operation absorbed a much smaller amount. Pratt with Falcon-Lesses and Herschenson³⁵ (1931), giving particular attention to the dogs—a carefully regulated diet which was given in frequent small feedings and included vitamins, as well as plenty of sunshine, exercise, etc.—found that practically normal absorption took place at times in both depancreatized dogs and animals with their ducts ligated without the addition of pancreas in the diet. These animals, however, showed a labile digestive ability and at other times passed the typical large, bulky "pancreatic" stool.

In a further attempt to analyze this situation Pratt directed Handelsman and Golden³⁷ (1934) to study three dogs with their pancreatic ducts ligated to observe the effect of varying the food components and of varying the quantity of food ingested on the absorptive ability of the animals. No definite relation to the type of food ingested was found. Large quantities of food when given were absorbed in the absolute sense but showed a relatively greater amount excreted in the feces. Furthermore, the animals could not tolerate very large diets for longer than two weeks before an enteritis occurred which responded to treatment when smaller diets were given. They were led to conclude that factors which are as yet unknown influence absorption since not only did the same dog respond differently to the same diet, but different dogs under the same experimental conditions responded in an irregular fashion. The exact role of the vitamins added to the diet, a factor neglected by the earlier workers, is not known. Nasset, Pierce and Murlin³⁸ (1931) showed that there is no effect of yeast on the amount of nitrogen excreted through the feces in depancreatized dogs. The work of Mottram, Cramer and Diew³⁹ (1922) showing by histological studies that vitamins hasten fat absorption, has not as yet been studied in animals without pancreatic juice. However, both Pratt and Ivy⁴⁰ have been impressed with the marked importance of vitamins in their experiments particularly in maintaining the animals in good health and with good fat absorption.

THE LENGTH OF LIFE OF ANIMALS WITHOUT EXTERNAL PANCREATIC SECRETION

Experimenters working with depancreatized dogs reported that these animals died of inanition although they ate large amounts of food and their glycosuria was controlled by insulin. This group of workers did not chemically analyze the stools and reported "tremendous amounts" of fat in the stools microscopically. Since quite early it was found that life could be prolonged in these animals by including raw pancreas in the diet, it was assumed that enzymatic action was the beneficial factor. In 1924 Fischer⁴¹ and Allen, Bowie, McLeod and Robinson⁴² pointed out the importance of fatty infiltration of the liver in these animals as a cause of death. Further studies by Hershey and Soskin⁴³ (1932) and Best⁴⁴ (1934) and his co-workers have revealed that lecithin and choline as well as the feeding of raw pancreas can prevent this. The literature on this subject has recently been reviewed by Greene, Handelsman and Babey⁴⁵ (1937).

Berg and Zucker⁴⁶ reported fatty infiltration of the liver following pancreatic fistulae. A perusal of many autopsy records of dogs with ligated pancreatic ducts studied by J. H. Pratt (unpublished) reveals no case with evidence of abnormal infiltration of the liver with fat. This coincides with the experience of Von Prohaska, Dragstedt and Harms⁴⁷ (1936) who also find no relationship between the deprivation of the external secretion of the pancreas and fatty livers. Bloom and Handelsman⁴⁸ reported a case of a young dog with naturally occurring diabetes which died because of fatty changes in the liver (jaundice, etc.). The acinar tissue was for the most part well preserved and stool studies revealed no evidences of pancreatic secretion deficiency, but practically no islets of Langerhans were found. An internal secretion of the pancreas which prevents the occurrence of fatty livers has actually been isolated by Dragstedt, Von Prohaska and Harms⁴⁹.

Absence of the external secretion of the pancreas from the intestine does not seem incompatible with a fairly long and healthy life. Several of J. H. Pratt's dogs with ligated ducts lived for long periods of time. "Zep" lived for over three years and "Nellie" over 2½ years without ever being fed pancreas or enzymatic preparations.

Complete pancreatic fistulae with continuous loss of the secretion outside the body leads to death in five to eight days. The mechanism leading to the fatal ending in these cases has been studied by Elman and McCaughan⁵⁰ and others,⁵¹ and has been found not to be related to the digestive function of the pancreatic secretion but to the acid-base economy of the animal. Large quantities of physiological saline administered to such dogs can prolong their lives for a longer period of time.

THE DIGESTION AND ABSORPTION OF FATS IN THE ABSENCE OF PANCREATIC JUICE

The pancreas played the rôle of "star witness" in the earlier arguments of the physiologists as regards the necessity of the splitting of fats before

absorption. However, fat recovered in the stools is for the most part well split even when the greatest source of lipase, the pancreatic juice, is absent from the intestine. This fact was first noted in the first animal experiments of Abelman¹¹ in 1890 where depancreatized dogs were used. Pratt, Lamson and Marks²⁶ (1909) also found excellent hydrolysis of the fats in the stools of animals whose pancreases were allowed to remain in the body with the pancreatic ducts blocked, for example, one of the dogs studied excreted 88.7 per cent of the ingested fat in his stools and 70 per cent was in the form of fatty acids and soaps. H. Wendt⁵² in his review has collected the clinical literature on this subject with the same conclusions.

The factors involved in the mechanism of this excellent fat splitting in the absence of pancreatic juice have been puzzling. Three other sources of lipolytic activity have been known to exist. Volhard⁵³ clearly established the presence of a fat hydrolyzing enzyme in the stomach which is active in acid medium, and Boldyreff⁵⁴ (1905) demonstrated an enzyme of similar nature in the intestine. It has been known that many bacteria also have the power to split fats particularly in the colon.

Umber and Brugsch⁵⁵ (1906) interested themselves in this problem first suggested that the gastric lipase might play a rôle when there was a deficiency or absence of pancreatic juice. They reported a single observation on sacrificing a depancreatized dog, the fat collected between the pylorus and papilla was only 18.2 per cent split whereas that in the lower ileum was 42 per cent split. This made them minimize the importance of the gastric lipase and led to search for lipase in other organs.

Gross⁵⁶ (1912) in studying two cases where atrophy of the pancreas was clinically diagnosed (one case later proved at autopsy) searched for a cause of the excellent splitting of fats in these cases. He found in these patients that gastric juice when left with neutral fat in an incubator at 38° for an indefinite length of time split the fats. Since this did not occur when toluol or chloroform was added, he supposed that bacterial action in the stomach and upper intestine caused these results.

Nothmann and Wendt⁵⁷ in 1931 criticizing Gross' results instituted experiments on five depancreatized dogs to which they fed olive oil test diets. The dogs were killed from four to eleven hours after having been given the test diets and the fats in the small intestine were analyzed quantitatively and for the amounts hydrolyzed. They found only 2.01 per cent to 3.98 per cent of the fats in the small intestine split whereas in the large bowel 14.82 to 22.11 per cent were in the form of fatty acids and soaps. This led them to emphasize the lipolytic activity of the bacteria in the colon. In two of their experiments wherein the total fats remaining in the intestinal canal were determined, they were able to recover 89 per cent of the ingested fat in one case and almost 100 per cent in the other. The amount of fat absorbed as well as the poor splitting stands in contrast to the experiments where excellent absorption of fats has been found when balanced diets are

fed to the animals We have tabulated from reports in the literature the results of analyses of intestinal contents of dogs killed after a normal meal and have included some unpublished results obtained by J H Pratt (table 2)

TABLE II

% Split in	Normal Dogs			Depancreatized Dogs		Dogs with Pancreatic Ducts Ligated
	Starling and Pincussen	Abelmann	Umber and Brugsch	Umber and Brugsch	Pratt (unpubl)	"Toby" Pratt, Golden and Handelsman (unpubl)
Stomach	30-40%	—	—	—	—	31 3%
Duodenum	—	—	30 2%	18 2%	—	32 3%
Jejunum	—	32%	—	—	41 5%	—
Ileum	—	57%	48 9%	42 0%	46 4%	31 9%
Colon	—	76%	81 0%	72 9%	—	45 0%
Stools (same diet)	—	—	—	—	—	51-55%

A careful analysis of the factors that contribute to these opposite results obtained with olive oil administration in contrast to balanced diets revealed interesting results Nothmann and Wendt ⁵⁸ found that after iodipin and egg yolk mixtures, roentgen-ray studies in depancreatized dogs showed enormously rapid gastric emptying time They checked this observation with quantitative chemical analyses of the gastrointestinal contents of depancreatized dogs killed at various intervals after being fed olive oil test meals Independently, Beguria working in the Tufts College Physiology Laboratory with olive oil-barium sulfate mixtures obtained similar results in roentgen-ray studies of depancreatized dogs, in some dogs, the olive oil mixture was in the ileum in one hour with complete emptying of the stomach by that time

Unpublished roentgen-ray studies by Pratt done in 1917 revealed only very slight changes in the gastrointestinal motility of several depancreatized dogs and animals with their pancreatic ducts tied These studies were done with plain barium sulfate suspensions or with ordinary canine diets mixed with barium This was substantiated by other methods In practically none of our dogs did carmine appear in the stools before 15 hours, usually 24 hours Furthermore on sacrificing one dog four hours after a meal 58 per cent of the food was still in the stomach and only 11 per cent was in the proximal colon Yesko ⁵⁹ and Fauley and Ivy ⁶⁰ found a slightly decreased gastric emptying time in such dogs, the latter attribute this as due to a normal hunger mechanism

Dr Beguria was kind enough to do gastrointestinal series on two of our dogs with ligated pancreatic ducts With ordinary barium sulfate suspension in water, a practically normal motility was found, but with the olive

oil-barium sulfate mixture, an extremely rapid gastrointestinal motility was demonstrated. This latter result stands in contrast with the work of Nothmann and Wendt⁵⁸ who did not find the rapid passage of the olive oil in dogs with ligated pancreatic ducts but only in depancreatized dogs. Because of their findings, they proposed the theory that an internal secretion of the pancreas regulates gastrointestinal motility. The studies of Pratt and Beguria do not offer warrant for such a theory.

The unusual acceleration of the passage of olive oil and iodipin through the intestines, a condition which does not occur with usual diets in the absence of pancreatic juice, explains the extreme differences in digestion and absorption found by Nothmann and Wendt⁵⁷ and other workers. This specific "diarrhea" of the oils does not allow sufficient time for their splitting and absorption. This difficulty does not exist with other foods.

The problem of how the fats of usual diets are split in the absence of pancreatic lipase cannot be explained entirely by slow intestinal motility. A perusal of table 2 reveals that a considerable amount of fat is already split in the stomach (25 to 30 per cent) in both normal and depancreatized dogs. Careful control studies by Pratt and Golden (unpublished) revealed that the diets of dogs in the Tufts laboratory were in some instances already 10 to 15 per cent split before ingestion. This was traced to the use of cans of Klum opened for a time before use. In other unpublished experiments, the gastric contents of two dogs with ligated pancreatic ducts were analyzed four hours after feeding and yielded 23.5 per cent to 27.2 per cent of the fats in the split form. Although this is minimal when compared to the 40 to 50 per cent splitting usually found in the ileum, the gastric lipase may really be of some significance. Pratt, Golden and Handelsman (unpublished) studied the pH of the intestinal contents of dogs without pancreatic juice who were killed four hours after a meal. The hydrogen-ion concentration showed strong acidity throughout. The studies of Hoerner⁶² showed that normally the pH of the duodenal content may range from 7.81 to as low as 3.31. In dogs without pancreatic secretion, although the range found was within these limits, the lower hydrogen-ion values were most often found. Since the gastric lipase hydrolyzes fats optimally in an acid medium, its action may possibly be carried on in the lower intestinal canal in the absence of pancreatic juice.

Minkowski⁶³ (1890) expressed the belief that an intestinal lipase hydrolyzes the fat. However, the importance of intestinal lipase is minimized by Hull and Keeton⁶⁴ who find the concentration of gastric lipase five times greater. Also Koskowski and Ivy⁶⁵ (1926) found no change in the *succus entericus* in the absence of pancreatic juice and Fauley and Ivy⁶⁶ found a hypersecretion of gastric juice under those conditions.

The other locus of lipolytic activity, the colon, does not seem to be important regarding fat absorption. Nakashima⁶⁶ (1914) and Verzár⁶⁷ (1937) have found no evidence of the ability of the colon to absorb fat although Yamakawa⁶⁸ (1929) claims this to be possible.

Studies of fat absorption approached from other angles have clarified the rôle that fat splitting actually plays in the resorption of fat. Pflüger⁶⁹ (1901) had advanced the "saponification theory of absorption" and insisted that there must be complete splitting of fats before absorption could take place. On the other hand Mellanby⁷⁰ (1928), minimizing the importance of fat hydrolysis, showed that the amount of lipase in the pancreatic juice of a cat is so small that it could merely serve as a mechanism to initiate emulsification of the ingested fat by providing only a very small amount of soap. F. Verzar (1936) has reviewed the literature on this subject as well as his own works which have clearly demonstrated the importance of lipase and bile in fat absorption. He showed that neither fine emulsions of a neutral fat, nor neutral fat together with lipase, nor neutral fat emulsified with bile acids were absorbed from the intestines of dogs whose bile ducts were tied. But when neutral fats were put into the intestines along with lipase and bile acids, 74 per cent were absorbed after 24 hours. The bile acids do not act upon neutral fats, but they form physical complexes with fatty acids resulting in combinations which are more soluble and diffusible than either of the parent components and which are easily absorbed. These results have been confirmed by Riegel, Elsom and Ravdin.⁷¹

From these studies it can be seen why good fat absorption may take place in the absence of pancreatic juice as long as some lipolytic agent initiates the hydrolysis of neutral fats. The finding that an animal without pancreatic secretion entering the intestines may show good absorption at one time and poor at another time indicates that other factors as yet unknown must play a great rôle. Further studies must clarify the importance of vitamins, mineral content, the differences of various fats, etc.

Since the fatty acid-bile acid complexes described by Verzar⁶⁷ are broken down in a medium with a pH below 6, and since the pH of the intestinal canal of a dog without pancreatic juice can be as low as 3.5, another factor suggests itself for study. One would suspect that the administration of alkalis might aid fat absorption, but experiments by Poczka and Fischel⁷² on a patient with pancreatic insufficiency showed that such treatment actually increased fat excretion.

Experimental studies involving the administration of pancreas (fresh or extracts) to animals without pancreatic secretion have been contradictory and give no conclusive proof of the rôle played by pancreatic lipase. The consistent improvement obtained in the digestion of proteins and carbohydrates in such substitution experiments does not seem to hold for fat. Pratt, Lamson and Marks²⁶ believed they obtained better fat absorption after the administration of pancreatic extract. Nothmann⁸⁰ found marked improvement in fat absorption in depancreatized dogs when large doses of "pankrophorin" were given. Absorption studies in a patient with achylia pancreatica by Poczka and Fischel⁷² revealed that the majority of proprietary preparations in Germany with the exception of "Pancreatol-dispert," did not

prevent fat loss in the stools. Very recent experiments with depancreatized dogs by Selle⁸¹ using enteric coated as well as plain pancreatic extracts (potent in vitro) showed no improvement in fat absorption, although in the same experiments the nitrogen utilization was markedly increased. However, Selle who reported no benefit, had excellent (90 per cent) fat absorption even without the administration of pancreatic enzymes whereas Nothmann and Wendt who were impressed with the efficacy of oral pancreatin in depancreatized dogs had had previously only 43 per cent of the dietary fat absorbed. Similarly Sarzana⁸² who obtained only 50 per cent absorption of olive oil in pigeons with ligated pancreatic ducts, also noted improvement up to 84 per cent absorption when pancreatic juice was given along with the fat. These differences in reports of success in pancreas administration point again to the numerous complicating factors controlling fat absorption.

THE NATURE OF THE FAT IN THE FECES OF ANIMALS WITH PANCREATIC STEATORRHEA

Bloom, Sperry and their co-workers⁷³ have shown the lack of relationship between dietary fat and the fat excreted in the stools of normal animals. A Krakower⁷⁴ has shown this to occur also in humans. In normals, after all the dietary fats are absorbed, apparently fat is again excreted by the intestines to form the fecal lipoids which are entirely independent of the food ingested.

Studies in Pratt's laboratory by Krakower and Rosenblum (unpublished) revealed a close similarity of the fat in the stools of animals deprived of pancreatic juice to the dietary fat. When fed olive oil, the iodine number of the fecal fat approached that of olive oil, when butter was fed, the iodine number of the fecal fat approached that of butter.

The external pancreatic juice has been found by Tangl and Berend⁷⁵ (1930) and Tangl⁷⁶ (1932) to contain a "dehydrogenase" which is activated by bile. Berend⁷⁷ (1933) demonstrated such an active enzyme in the pancreas alone and Quagliariello⁷⁸ isolated a desaturating enzyme in bile alone. Artom⁷⁹ has reviewed experiments by Italian workers demonstrating similar desaturation of fats by many tissues and even by *B. coli*. On the other hand, there is evidence that unsaturated fats may be preferentially absorbed. Apparently these factors did not influence the fats studied by Krakower and Rosenblum in the above experiments with dogs whose ducts were ligated. In other experiments where Nucoa was employed instead of butter or olive oil, the close similarity between ingested and excreted fats was not obtained, the latter being more unsaturated. It is possible that this difference was due to the presence of desaturating enzymes in the intestinal canal.

THE DIGESTION AND ABSORPTION OF CARBOHYDRATES IN THE ABSENCE OF PANCREATIC JUICE

Clinically it was maintained by F. Mueller that the digestion of starches was not necessarily impaired in the absence of pancreatic secretion. Furthermore, studies on "intestinal catarrh" and cases with increased gastrointestinal motility due to causes other than pancreatic disease have shown large amounts of carbohydrates in the stools. Thus the presence of starch in the stools has been more or less neglected by the clinicians as a comparatively insignificant factor in the absence of pancreatic enzymes in the intestine.

Rosenberg¹⁵ in 1896 pointed out the presence of starch in the stools in these cases. It is only recently that this problem has been studied experimentally. Dogs lend themselves well to this study since their saliva contains no ptyalin. Hjort³⁵ working in Pratt's laboratory studied normal dogs on a comparatively large diet of ground meat, cracker meal, butter and vitamins and found the stools to contain only 1.08 per cent starch (analyzed as sugar), the same animal after the pancreas had been completely separated from the intestine passed stools containing 14.23 per cent starch (as sugar). Handelsman, Golden and Pratt (unpublished data) found the stools of two dogs with similar operative interference to consist of 0 per cent to 9.1 per cent carbohydrate (analyzed as sugar) when diets low in carbohydrates were fed, and to contain 21.5 per cent to 46.6 per cent sugar when high carbohydrate diets were fed. Beazell, Schmidt and Ivy⁸³ fed dogs with the pancreas separated from the intestine with diets containing 62 per cent starch, and they found that 18 per cent to 39 per cent of the stools consisted of starch. Sekikawa⁸⁴ found that feces of normal animals contain 80 to 190 mg carbohydrate per gram of stool, after ligation of the pancreatic ducts the carbohydrate concentration of the stools rose to 190 to 230 mg per gram of stool while after pancreatic fistula the concentration was still higher, 240 to 500 mg per gram of stool.

Studies of the percentage of starches in the stools do not give a true picture of the amount actually absorbed. A good example of this occurred in the dog "Nellie" where Pratt and his co-workers found after a high carbohydrate meal absorption of 92.6 per cent of the ingested cracker meal, yet stool analysis showed 30.1 per cent of the feces to consist of carbohydrate. For the most part, carbohydrates seem to be more than 90 per cent absorbed, when the intake is not too excessive even in the absence of pancreatic juice and this good absorption seems to be independent of the relative fat and protein content of the diet.

To explain this good absorption, recently Zucker, Newburger and Berg⁸⁵ (1932) again renewed the theory of Rosenberg¹⁵ that the pancreatic enzymes may be secreted by other organs. These workers studied the increased serum and urinary amylase in dogs whose pancreatic ducts were blocked and were impressed with the fact that the disappearance of the in-

creased serum amylase is not accounted for by its excretion in the urine. They report evidence of increased amylolytic activity of the bile in cases where the pancreatic ducts have been tied. This was first demonstrated in birds by Langendorff⁸⁶ in 1879. This type of compensatory mechanism was also studied by Schegalow⁸⁷ in 1902 who reported increased proteolytic activity in the bile after ligating the pancreatic ducts and Lombroso¹⁷ (1906) who found the same for lipase. Pfluger⁸⁹ (1905) expressed his approval of this theory. However, the excellent absorption of carbohydrates reported by Pratt³⁵ in dogs with the pancreas removed from the body does not allow much importance to be attached to this theory.

Beazell, Schmidt and Ivy⁸³ found that administration of pancreatin as well as other diastase preparations markedly decreased the amount of carbohydrate in the stool of dogs with their pancreas completely disconnected from the intestine. Such excellent therapeutic results would tend to substantiate the impression that it is actually the absence of diastatic digestion in depancreatized dogs that leads to the excretion of carbohydrates in the stools rather than other causes such as rapid gastrointestinal motility, improper pH of the intestine or interference with the absorptive processes.

That the compensatory mechanism of carbohydrate digestion can be strained in some cases by the excessive administration of starchy foods was shown by one of Pratt's dogs³⁵. This animal was unsuccessfully operated upon and not all the pancreatic ducts were ligated as was proved at autopsy and also noted clinically by the absence of the typical "pancreatic stools". Whereas fat and nitrogen were normally absorbed, large quantities of starch appeared in the stools. Apparently in this case of hypochylia pancreatica, the amount of pancreatic juice was insufficient for the complete digestion of carbohydrates.

THE DIGESTION AND ABSORPTION OF NITROGENOUS FOODS IN THE ABSENCE OF PANCREATIC JUICE

In normal animals, the amount of fecal nitrogen does not vary with changes in the amount of ingested nitrogen, and even remains the same on a protein-free diet. The fecal nitrogen may be increased by raising the indigestible, non-nitrogenous bulk of the diet while changes in the digestible food components have practically no effect⁹⁰. It would seem that the fecal nitrogen originates in a manner similar to that of fecal fat, namely as a secretion product of the bowel rather than being a true indigestible residue.

In dogs without pancreatic juice entering in the intestine, usually 35 per cent to 55 per cent of the ingested nitrogen is excreted in the stools. Similar results have been obtained in cats by Greenberg⁹¹ who found 33.2 per cent to 48.8 per cent excreted. Occasionally higher values are obtained (see table 2). That this increased fecal nitrogen represents the undigested food nitrogen has been recognized by clinicians by tests with cell nuclei and striated meat fibers found in the stools after the ingestion of meat. Detailed

chemical studies of the type of nitrogen found in the stool of depancreatized animals have not been made probably because of the difficulty in controlling gastrointestinal motility as well as bacterial putrefaction in the colon (Review by Pratt⁹²) There is also a lack of data concerning the intermediary protein breakdown products in the intestine in the absence of tryptic digestion, a phase in which the gastrointestinal allergists are now interested

F. G. Benedict and Pratt²⁷ studied the specific dynamic action of meat feeding in dogs in which the pancreatic secretion was absent After the feeding of 500 grams of meat, the 24 hour increment in CO_2 production was 28 per cent for a normal animal, compared to 17 per cent and 22 per cent in experimental animals, after 750 grams of meat the increase in metabolism in a normal dog was 62 per cent as compared with 48 per cent, 43 per cent and 25 per cent in animals without pancreatic secretion Kúthy⁸⁸ by direct experimentation in normal rats has established that the specific dynamic action of proteins parallels their absorption rate The data of Benedict and Pratt on closer examination reveal that the increased CO_2 production of the experimental animals after meat feeding as determined over four hour periods, approximately parallels that of the control animal with the exception that there was a diminution in the quantity produced Since the animals were in nitrogen balance, it would seem that protein absorption in animals without pancreatic juice proceeds normally except for the decreased amount of absorption

The problem of nitrogen balance in depancreatized dogs has been studied by Nasset, Pierce and Murlin³⁸ who showed that such dogs may have an increased nitrogen retention or normal balance even when large quantities of nitrogen are lost in the stools

An interesting problem has been brought up by the work of Selle⁸¹ who found that pancreatin administration reduced the weight of the stools of depancreatized dogs by 50 per cent and reduced the fecal nitrogen 35 per cent to 65 per cent Fat excretion in these animals, 10 per cent to 11.4 per cent, was almost normal, and was uninfluenced by pancreatin administration Since no carbohydrates were fed to these animals during the metabolism periods, it would seem that the reduced bulk of the stools after pancreatin paralleled the decreased nitrogen excretion This observation is interesting inasmuch as the bulkiness of the pancreatic stool is one of its typical features A perusal of the fecal analyses by Handelsman, Golden and Pratt³⁷ reveals a relationship between increased nitrogen ingestion and the increased dried weight of the stools, but the bulkiness did not seem to depend upon an increase in the percentage of nitrogen in the stool or on the percentage of nitrogen absorbed The enormity of the "pancreatic stools" has not been completely explained Incomplete studies in Pratt's laboratory with the diets used would seem to indicate that the dried ash content of the stools is not the cause of the large size of the feces On calculating the results of many careful dried stool analyses there has been found an "un-

determined residue" when the carbohydrates, fat, ash and proteins ($N \times 6.25$) have been totaled. This undetermined residue is probably greater than calculated since a part of the nitrogen in the stool is not from protein.

CONCLUSIONS

Care must be used when studying the literature concerning the external secretion of the pancreas. The earlier studies reported good absorption of food when the pancreas was separated from the intestine and attributed this to an internal secretion of the pancreas regulating absorption. However, these conclusions were based on experiments where the pancreatic juice was not completely excluded from the intestine. After more careful surgical interference the same digestive disturbances were found as after pancreatectomy. Although the early experiments showed rather poor absorption of foods, in later studies employing smaller feedings, including vitamins, and giving more care to the general well-being of the animal, fairly good absorption of foods occurred. In contradiction to the good absorption of the unsuccessfully operated dogs, the animals actually without pancreatic secretion in the intestine show a labile digestive mechanism good at times and poor at other times. Only in the carbohydrate fraction does this lability seem to depend on the diet as manifested by a higher percentage of carbohydrate in the stools. The nitrogen and fat absorption are also labile, but the factors causing these variations are not completely understood. Fat digestion and absorption are particularly complicated. The duty of the pancreatic juice seems to be to split the neutral fats in preparation for the absorption of the fatty acids combined with bile acids. In the absence of the pancreas a compensatory mechanism splits the fats, the gastric lipase may play some rôle in this. The significance of the lowered pH of the intestinal canal in the absence of pancreatic juice as well as a singularly rapid gastrointestinal motility when oils are fed is not as yet known. Most of the digestive and absorptive phenomena found in depancreatized dogs are found in dogs with their pancreatic ducts ligated. The internal secretions postulated to explain fat absorption or to regulate gastrointestinal motility are not substantiated. The fatty infiltration of the liver in depancreatized dogs, however, seems to be related to an internal secretion of the pancreas.

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CASE REPORT

THE SYNDROME OF DYSPHAGIA AND ANEMIA

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"THERE is a variety of dysphagia, not uncommon in middle-aged women, which in all cases presents almost identical signs and symptoms and which reacts uniformly to treatment, but as to the pathology of which we are ignorant." This statement by Brown Kelly¹ in his original discussion of the subject is still true of the syndrome he described. Kelly¹ and Paterson,^{2,3} in 1919, outlined the symptom complex of "spasmodic dysphagia" as one clearly distinct from that of "globus hystericus," achalasia of the cardia or organic obstructive lesions of the esophagus. Their patients were women, the majority of whom were between 40 and 50 years of age. The outstanding symptom in each patient was either a slowly or a rapidly appearing dysphagia, referred to the level of the larynx, in the absence of any previous chemical or thermal esophageal injury. Several patients related symptoms common to the neuroses. Most of them were undernourished. Both authors found a pallor of the pharyngeal mucous membrane, the tongue surface smooth and devoid of papillae. The mouth corners were fissured, there was notable pyralism. In several patients an easily ruptured membrane extended transversely across the entrance to the esophagus. In others there were firm, approximated bands in the mucosa forming a closure of the gullet at the site of the complaint. These bands apparently were not on a cicatricial base and yielded readily to pressure from a tube, bougie, or endoscopic instrument. In many instances there seemed to be simply increased muscular tone at the entrance into the esophagus. The patients had no intermittent symptoms or other characters of hysteria. Dilatation maneuvers gave the patients definite relief and Kelly concluded, from a particular study of 10 patients, that the disorder was a spasm of esophageal muscle developing as a result of faulty innervation, probably failure of a proper local reflex arc through the plexuses of Auerbach and Meissner.

Vinson,⁴ in association with Plummer, after observations on 69 patients (only 12 were males) was impressed with the occurrence of an anemia of the hypochromic type in dysphagia. The onset of the disease in the majority of his patients was marked by a rather sudden hindrance in swallowing solid food. The symptoms often were tolerated for years before a physician was sought. Roentgenographic and esophagoscopy examination gave no evidence of disease. Twelve of these patients had palpable spleens. The passage of an esophageal sound gave excellent results when followed by Bland's pills, Fowler's solution and encouragement to eat. Vinson was impressed also by the hysterical manifestations of these patients. Since this report in 1922, the disorder frequently

* Received for publication April 22, 1937. From the Golden Clinic, Davis Memorial Hospital, Elkins, West Va.

has been called the Plummer-Vinson syndrome. Moersch and Connor⁵ collected a series of 65 such hysterical dysphagias, all being found in women between the ages of 23 and 63 years.

Hurst⁶ reported a case which suggested that infection of the throat, as by streptococci, might give rise to a reflex spasm in the esophagus. Ryle⁷ reported a patient having no delay in the passage of barium and in whom he felt hysteria was the etiologic factor. Cameron^{8, 15} reported an analysis of 25 case studies. He emphasized the smooth, pale, dry mucous membrane of the mouth and fissures extending from the mouth corners over the skin. All of his patients were women between 41 and 60 years of age. The dysphagia usually was located at the level of the larynx. Splenomegaly was found in eight instances. In 15 patients, the hindrance in deglutition appeared to have preceded the anemia. Cameron considered atrophy of the mucous membrane, with the probable loss thereby of both mucous secreting glands and properly functioning sensory nerve endings, as of great significance in the mechanism of the dysphagia. Jones and Owen,⁹ in summarizing the clinical characters of the disorder, were impressed by the long duration (one to eight years, in their experience) of the dysphagia. Evans,¹⁰ considering the disorder not a local disease but a local manifestation of a general disease, presented incomplete evidence that syphilis may have been the causative factor in some instances. He referred to a necropsy on one patient but gave no details as to the microscopic findings in the esophagus. Witts¹¹ described anemia and dysphagia in 13 women with characteristic findings and excellent response to therapy with iron. The anemia was definitely microcytic in all but one patient.

Suzman,¹² in 1933, reviewed the previously reported cases and added eight from his experience. One of his patients died following perforation of the esophagus by an unguided filiform bougie. In an autopsy on this patient, the sections from the esophagus showed marked desquamation of the superficial epithelium and a few areas of unequivocal keratinization. There was moderate infiltration by lymphocytes and plasma cells. The musculature was atrophied. Of greatest importance was his observation that there were no demonstrable changes in the nerve plexuses. Hoover¹³ reported on a series of 17 cases, in seven of which a definite band or web was found in the upper end of the esophagus. He observed that the passage of the esophagoscope alone relieved the dysphagia in most instances. McGibbon,¹⁴ from a study of seven such patients, emphasized a characteristic glossitis, stomatitis and atrophic pharyngitis as the essential findings. Splenomegaly, koilonychia, achlorhydria, fissures at the angles of the mouth, brownish discoloration of the skin and increased fragility of the erythrocytes were occasionally associated with the syndrome. Five of his patients had a web or other demonstrable upper esophageal lesion.

Many of the reported histories indicate that dysphagia precedes the onset of anemia but occasionally the reverse is true.¹⁵ Patterson³ stated that the anemia comes late in the disease and is to be regarded as a secondary manifestation of the dysphagia. Benhamou and Cohen-Solal¹⁶ regarded the entire symptom complex as being secondary to an essential hypochromic anemia.

Proper consideration of dysphagia resulting from a failure of the introitus of the esophagus to receive and adequately transmit solid food and fluids, requires a careful elimination of palpable lesions which may give similar symptomatology. Such recognized causes of obstruction are retropharyngeal ab-

sciss, bulbar paralysis, pharyngeal, laryngeal or esophageal neoplasm, congenital malformation, foreign body, cicatricial contraction, pulsion or traction pouch, mediastinal mass, and others carefully listed by Hutchison¹⁷ Impaired deglutition has been noted in patients with scleroderma, progressive muscular dystrophy,¹⁸ exostoses of margins of cervical vertebrae,¹⁹ and unilateral pulmonary fibrosis²⁰

Since the treatment of this well identified clinical syndrome has been remarkably successful, rarely does an opportunity for postmortem study appear There have been found but two previously reported autopsies on patients who had the clinical syndrome of idiopathic dysphagia and anemia^{10, 12} The patient in the following case report had no demonstrable cause for dysphagia The pressure of the thyroid lobes on the esophagus was associated with normal deglutition for too long a time for it to serve as an explanation of dysphagia The age of the patient when her symptoms appeared and the manner of her death, exsanguination by bleeding from multiple points in the gastrointestinal tract, are unusual

CASE REPORT

Mrs E H, aged 66 years, entered the Davis Memorial Hospital, January 17, 1936, complaining of loss of weight and weakness for the previous six months and of dysphagia for six weeks The embarrassment in deglutition was slight until January 14 For the few weeks prior to the latter date she observed that both liquid and solid foods were swallowed with some difficulty Three days before admission her son observed that she seemed to be unable to take any of her food and that saliva drooled from her lips as she attempted to swallow She left the table in the middle of the meal and took little or no nourishment during the next two days She complained of no fatigue in mastication There was a known loss of 30 pounds in weight in the six months prior to her hospital admission

The patient had been in apparent good health previously, save for a few aching pains, of the type associated with hypertrophic arthritis, in the lower back and thighs since the age of 60 years The menses ceased at the age of 40 years Her mother died at the age of 58 years with a clinical diagnosis of carcinoma of the stomach

The patient was cachectic, weighing but 81 pounds, and could scarcely walk from weakness Her skin was generally atrophic and loosely attached to the body Several fissure-like wrinkles radiated from each corner of her mouth A nodular but fairly symmetrical enlargement of both lobes of the thyroid was noted One pea-sized, moveable lymph node was palpable in the right supraclavicular fossa All upper teeth had been removed, a few worn teeth remained in the lower jaw The buccal mucous membranes were dry, the tongue surface was notably smooth as in atrophy of the lingual papillae There was no evidence of paralysis of any of the cranial nerves The skeletal reflexes were unchanged The abdomen was scaphoid in contour The thorax was moderately hyperresonant The heart sounds were faint, there was a systolic murmur of low intensity and short duration heard over the apex The blood pressure was 138 systolic and 96 diastolic

In the presence of the physician, the patient seemed unable to initiate the act of swallowing At each attempt, after bobbing her head a few minutes, she sought to expectorate soft food and water alike In the fluoroscopic room, the thick barium mixture accumulated in a peculiar round mass, the size of a golf ball, immediately below the level of the cricoid cartilage The patient was unable to move the bolus farther and, after being subjected to strong reassurance and persuasion for five minutes, regurgitated the mass She could not be induced to attempt to swallow the barium again When an effort was made by one of us (T M G) to pass the eso

phagoscope the instrument was firmly grasped in the upper esophagus. The view obtained was that of a swollen, hyperemic mucosa filling the end of the esophagoscope in every maneuver and, with the degree of force considered safe, the endoscope could be passed no farther.

The urine contained a trace of albumin. The blood had a hemoglobin value of 56 per cent (Sahl), 3,720,000 erythrocytes per cubic millimeter, and a negative Kahn reaction.

The patient was fed twice daily for four days by gavage through a heavy Ewald aspirator tube. In the first feedings the tube had to be forced through the upper

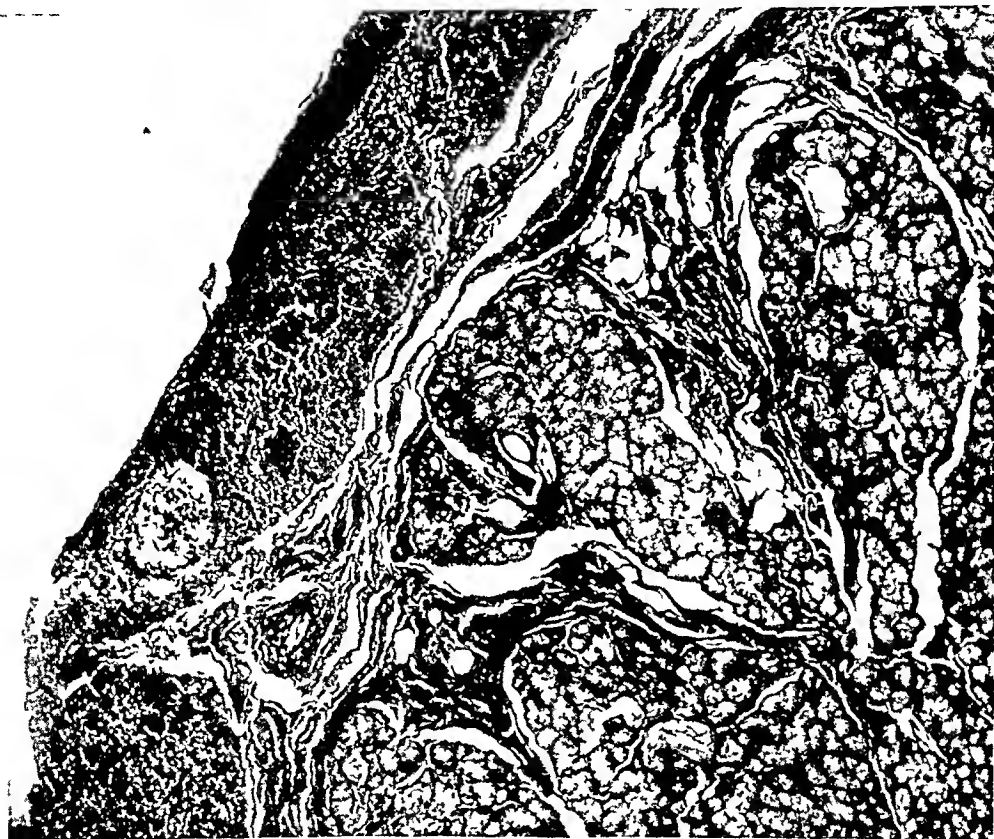


FIG 1

esophagus with more than the customary manipulation and pressure. By the third day the Ewald tube could be passed with distinctly less effort. At no time was free hydrochloric acid found (histamine was not used). The patient expectorated large amounts of mucoid saliva, requiring a cup constantly at her bedside. After the fourth day in the hospital she could swallow both soft food and liquids, the former more readily. The patient gained in strength and left the hospital January 25, eight days after admission, with instructions to take seven grains of reduced iron three times each day.

After seeming to improve for four days at home, the patient, on January 29, suddenly became very faint, dizzy, and fell to the floor. She had to be helped to her bed by her daughter. There was no loss of consciousness and no evidence of paresis of any extremity. After an hour in bed, she was well enough to be up and about the bedroom again but she complained of a vague abdominal discomfort.

She was given an enema and returned a tarry, offensive stool. During the night she made, alone, two trips to the bathroom. It is not known whether she defecated. The following morning the patient ate a small breakfast and again complained of marked dizziness and weakness. An hour or so after breakfast, she vomited a moderate amount of dark coffee-ground material which her daughter, a graduate nurse, recognized as blood. The patient made a 15 mile trip by ambulance to the hospital, losing consciousness five minutes before admission. Within an hour she had ceased breathing.

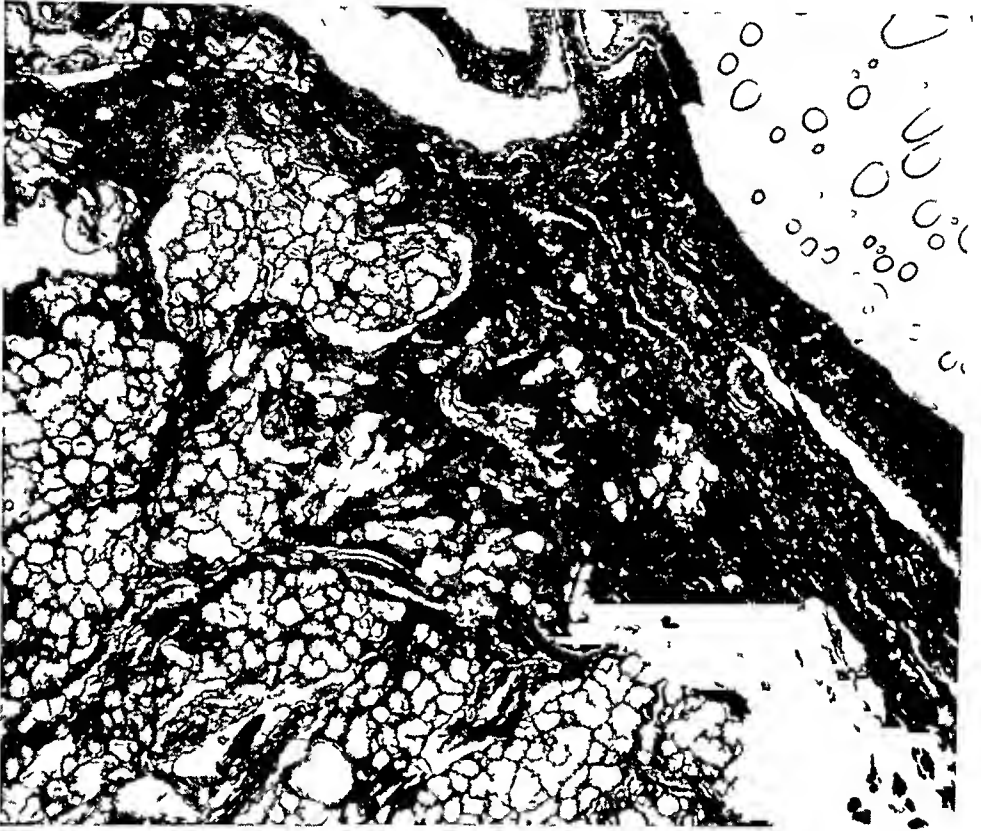


FIG 2.

A postmortem examination was started 30 minutes after death. There was a minimal quantity of panniculus adiposus. The distended intestinal loops were speckled fairly generally with subserous hemorrhages, 2 to 15 mm in diameter. The small intestine yielded 500 cc of clotted blood and bloody fluid. An equal quantity was found in the stomach. Innumerable bleeding points, not over 2 mm in diameter, were present in the mucosa of the upper jejunum, duodenum and stomach. No other lesion could be demonstrated in the abdominal viscera save for recent hemorrhages into both adrenal glands. The spleen was small, the liver of average size.

The heart weighed 290 grams. There were a few atheromatous plaques in the proximal aorta. The coronary arteries were patent. The mitral valve leaflets were scarred and fused so as to admit but one finger into the valve. The mitral annulus measured 70 cm in circumference. Other cardiac measurements were normal. The lungs showed no significant alteration.

In the lumen of the esophagus at its lower end was one-half of an insufficiently masticated stewed prune. There was no obstruction at the cardia. The inner surface of the upper half of the esophagus was hyperemic and had numerous irregular areas, 4 to 10 mm across, which were denuded of mucosa. There was no demonstrable obstruction. The entire esophagus, with the tongue and stomach attached, was removed for examination. The thyroid lobes were each approximately 3 by 3 by 5 cm, extended posteriorly beyond the trachea and left definite imprints upon the lateral surfaces of the collapsed esophagus. The surfaces made by cutting the thyroid revealed small cysts and areas of calcification in the substance of the gland.

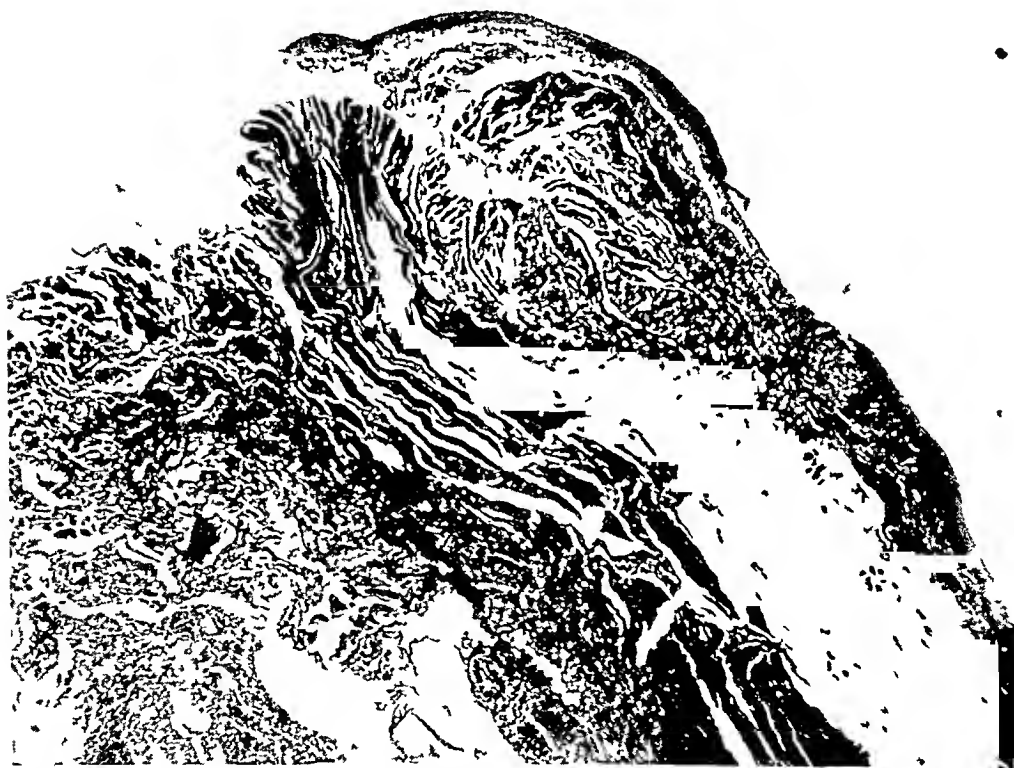


FIG 3

FIGS 1, 2, 3 Representative sections from the esophagus showing cellular infiltration, excessive development of mucous glands, denudation of epithelium and hypertrophy of the *muscularis externa*

Microscopic Examination Sections from the liver and spleen showed no change in structure. The wall of the stomach and small intestine had areas of hemorrhage beneath the epithelial lining, occasionally under the serosa and in the smooth muscle, but presented no other recognized change.

Mucous glands were plentiful in the sections from three blocks of tissue taken from the wall of the inflamed upper end of the esophagus. Cardiac type glands were scarce. There was no keratinization of the stratified squamous epithelium. The mucous and submucous layers were not atrophied but broken and denuded areas were clearly evident. Numerous oval islands (1 by 2 by 3 mm), predominantly of lymphocytes but with scattered plasma cells and polymorphonuclear leukocytes, lay beneath the epithelium. The muscular wall was of increased width, varying

from 3 to 6 mm, and showed excess fatty areolar tissue between the irregularly interlacing longitudinal and circular fascicles of striated muscle. Staining by Bielschowsky's silver method revealed no obvious change in the ganglia or fine network of nerves.

Dr G W Rake,²¹ who, with Hurst, originally described lesions in Auerbach's plexus at the middle and lower levels of the esophagus from patients having long standing achalasia of the cardia, has been kind enough to examine representative sections from the case under consideration. He stated in a personal communication, "I can find no lesions of the plexus or nerves. This, of course, does not rule out such lesions entirely since in milder degrees of achalasia one may find many normal Auerbach's plexuses to one abnormal one. My experience with cases of the Plummer-Vinson syndrome has been limited, but the one case which I have examined with care microscopically showed no lesions of the nervous mechanism."

The authors are likewise indebted to Dr Walter Brandes of the Pathological Institute of the University of Tennessee who, after examining the sections, reported, "A definite inflammatory reaction is present with moderate fibrosis and infiltration with lymphocytes. Also an infiltration with fat seems to be present in some areas in the musculature. It seems to me there are a rather large number of mucous glands present. They are unaltered except that in some areas there is a chronic inflammatory reaction as mentioned. The nerves that are seen in the sections I do not feel are noticeably altered. I do believe there is definite chronic esophagitis with erosion of the epithelial lining."

SUMMARY

The particularities of the syndrome of dysphagia and anemia, as observed by many authors, are noted. There is no proved pathological basis for the disorder. As such patients rarely come to the postmortem table, detailed gross and histological findings in one available case seem to be of more than passing interest.

Acknowledgment is made to Dr Angus K. Wilson, Davis Memorial Hospital, for preparation of the sections and to Mr Boyers M. Clark, Elkins, West Va., for the photomicrographs.

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EDITORIAL

PULMONARY EMBOLISM

IF anything is to be accomplished in the prevention and treatment of pulmonary embolism, several things are necessary. A much keener appreciation of its frequency, a knowledge of the chief circumstances that favor its occurrence, an ability to recognize it in its mild and nonfatal forms, and an aggressive and systematic program aimed at prevention, are essential minimal requirements.

The incidence of fatal pulmonary embolism in unselected consecutive postmortem examinations is above 2 per cent^{7, 13}. Pulmonary embolism accounts for from 5 to 6 per cent of deaths following surgical procedures^{12, 13}. In McCartney's series it accounted for about 5 per cent of deaths in parturition, for 3.32 per cent of deaths following trauma, and for slightly less than 2 per cent of all medical deaths¹³.

While the cause or causes of pulmonary embolism are still unknown, valuable studies have been made which indicate important factors in its production. Some of these seem capable of being attacked. These studies serve to identify the circumstances under which pulmonary embolism is likely to occur, and they thus permit us to concentrate our efforts on these groups. Pulmonary embolism is encountered chiefly in patients over 40 years of age². Abdominal surgery in general, and certain types of abdominal operations in particular, predispose to pulmonary embolism². Fatal pulmonary embolism is approximately twice as common among patients with cardiac disease as among patients with normal hearts^{5, 13}. Obesity has been shown to be an important factor predisposing to fatal pulmonary embolism¹⁴.

Pulmonary embolism rarely is due to detachment of the thrombus of thrombophlebitis². Conversely, when pulmonary embolism occurs, seldom are there signs of peripheral phlebitis. The commonest sites of thrombi giving rise to emboli are, in order of frequency, the iliac vein, the femoral vein, the pelvic veins, the prostatic plexus, the vena cava, and the right auricle¹². The infrequency with which an embolus arises in an upper extremity is striking in contrast to the lower extremity. The effect of gravity, and the much greater motility of the upper extremity, maintaining good venous pressure and promoting good venous blood flow, must be of paramount importance in accounting for this difference. Infection in the pelvic veins, thrombi produced by operations on the pelvic structures, which may extend into larger adjacent veins, and the fact that the venous return flow in the lower extremities is the first to suffer in any impairment of the circulation,⁶ are other factors accounting for the incidence of thrombosis in the lower extremities.

No exact knowledge is available to indicate the time at which a thrombus forms after operation. One suspects that the first 48 hours is a fruitful

period for thrombus formation. The systemic blood pressure is usually lowest during that period. Maximal immobilization of the trunk and legs occurs then. Fever, in itself capable of increasing the circulatory rate, usually is slight or has not appeared during that period. Can an embolus formed at that time be in situ for eight to ten days, the usual date at which fatal pulmonary embolism occurs? It is possible that during that period the embolus is slowly increasing in size, and because of its size and the increased force of the venous flow attendant upon increased activity at the eighth or tenth day, it is carried to the lung. On the other hand it may be that changes in the blood favoring coagulation⁸ reach their maximum from the sixth to the tenth day and determine the time of thrombosis and embolism. Actually, a combination of the factors of slowed venous return and alterations in the coagulating properties of the blood may constitute the most reasonable explanation.⁸

It is customary to regard marked dyspnea and cyanosis as the classical signs of pulmonary embolism. Dogmatic adherence to this conception results in failure to recognize many instances of this complication. Pulmonary embolism manifests itself frequently by the picture of shock. This is characterized by faintness, pallor, sweating, acceleration of the pulse, a marked fall in blood pressure, and sometimes by vomiting and collapse. A brief experience with pulmonary embolism teaches one that fatal attacks are preceded very frequently by milder, nonfatal seizures. The recognition of these premonitory attacks furnishes an incentive to vigorous attempts to prevent further attacks, and to increased caution in the patient's subsequent management. Certain electrocardiographic changes have been described which may assist greatly in the diagnosis of pulmonary embolism, and especially in its differentiation from acute coronary thrombosis^{3, 4, 14}. The patient who gives a history of previous pulmonary embolism following an operation calls for unusual care following subsequent surgical procedures. Even more than special categories of patients shown previously to have a high degree of liability to embolism, this group of patients with premonitory seizures warrants the most intensive studies in prevention.

On the basis that impaired venous circulation plays an important rôle in the occurrence of pulmonary embolism, the following postoperative regimen has been instituted by Gray and MacKenzie¹¹. The patient is placed in the Trendelenburg position for the first 24 hours after operation. Frequent inhalation of carbon dioxide, day and night during the first 48 hours, is instituted. Deep breathing exercises and encouragement of coughing are stressed. Extreme care is taken to keep the patient's legs warm at all times. Frequent massage of the legs is practiced during the first 48 hours and twice daily thereafter until the patient is out of bed. Passive and active movements of the extremities are carried out frequently during the time the patient is in bed. Attention to these details is especially important during the first 48 hours after operation. Experience to date¹

with this program encourages the belief that it is effective in preventing fatal pulmonary embolism *

The occurrence of a mild attack would seem to be a favorable setting for a trial of heparin. Whether a previous mild attack constitutes a contraindication to the continuation of the foregoing postoperative program, time alone will tell.

Why does death occur from pulmonary embolism? Arterial obliteration and insufficiency of the pulmonary circulation in the area involved are not satisfactory explanations. Reflex sympathetic inhibition was regarded by Villaret, Justin-Besancon and Bardin¹⁷ as being an important mechanism. Gosset, Bertrand and Patel¹⁰ submitted evidence that an embolus lodged in a peripheral vessel is fixed by arterial spasm. The rôle such a mechanism plays in the arterial insufficiency in arterial embolism has been discussed at length by McKechnie and Allen¹⁵. Is it not possible that pulmonary embolism results in spasm of some or all of the pulmonary arteries, thus explaining in part its serious consequences? On this ground, and on the basis of favorable results seen from its administration in embolic occlusion of the peripheral arteries,^{1,9} papaverine hydrochloride, grains $\frac{1}{2}$, might justifiably be administered intravenously immediately after a seizure suspected of being pulmonary embolism.

There are many unknowns in this complex problem, and this seems to have given rise to a feeling of impotency in attacking the situation that has stifled progress. There is reason to hope that if we utilize such knowledge as we now possess, as well as the results of future investigations, means will be found to diminish greatly this menace.

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* It is particularly difficult to evaluate the results of a program of prevention and treatment since fatal pulmonary embolism occurs in only 0.15 per cent of all operations and in 0.35 per cent of operations on the abdomen.²

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REVIEWS

Heart Failure By ARTHUR M FISHBERG, M D, Associate in Medicine, Mount Sinai Hospital, New York City 788 pages, 15.5 × 24 cm Lea and Febiger, Philadelphia 1937 Price, \$8.50

It is of course impossible to review in detail the subject matter of a book of this size. In 37 chapters the author discusses the phenomena of heart failure, peripheral circulatory failure and what he chooses to call hypodiastolic failure. In this last group are included those instances of inadequate diastolic filling of the heart such as may occur in pericarditis or tachycardia. In general he follows a scheme in which a symptom is described, the circumstances under which it occurs are explained, and the mechanisms involved in its production are discussed, descriptions of pathological anatomy are included when indicated. Left- and right-sided heart failure and failure initiated by "generalized cardiac strain" are discussed separately. The treatment of heart failure in general and in its special manifestations is discussed in further chapters. The literature pertaining to various aspects of the problems discussed has been reviewed and a bibliography is placed at the end of each chapter.

If it is kept in mind that further knowledge may modify the opinions expressed, this volume should serve excellently as a rather detailed examination of the subject.

W S L, JR

External Diseases of the Eye By D T ATKINSON, M D, F A C S Second Edition 718 pages, 15.5 × 24 cm Lea and Febiger, Philadelphia 1937 Price, \$8.00

This book, revised by the author, is the second edition, the first having been published by Lea and Febiger in 1934. Like the original, this edition is not limited to external diseases of the eye but includes those other conditions which may be diagnosed without the aid of the ophthalmoscope. The contents are divided into 15 chapters. Included in the chapter on diseases of the orbit is a consideration of nasal and sinus diseases which may secondarily involve the eye. As in the first edition many of the illustrations are of wax models, and while the majority of these are quite good, photographs of the actual lesion, especially if in stereopticon, would give a much better impression of the condition.

Valuable additions include description of slit-lamp microscopy, orthoptic training, allergic manifestations and some of the newer surgical procedures. Also included but rather underrated in value is the iridencleisis operation for glaucoma.

To the student, the general practitioner and the ophthalmologist this book certainly can be recommended.

H F G

Appendicitis, a Clinical Study By W H BOWEN, Hon M A (Camb), M S (Lond), F R C S 201 pages, 13 × 19 cm Cambridge University Press, London, Macmillan Co, New York 1937 Price, \$2.50

An interesting monograph by an English surgeon on acute and chronic appendicitis. The author advises immediate operation in the acute stage and sets up definite rules to govern the decision as to operation in the chronic stage. The author rightly stresses the importance of a knowledge of the macroscopic pathology of the appendix. The monograph is well written but does not constitute an important advance.

T R A

Handbook of Orthopaedic Surgery By ALFRED RIVES SHANDS, JR., B A., M D
593 pages, 15 × 24 cm C V Mosby Company, St Louis 1937 Price, \$5 00

This book by Dr Shands has been compiled to act as a ready reference book for advanced students and practitioners so that concise information may be at hand. No attempt has been made to go into details of description and analysis of the many problems, but rather to give the essentials of all orthopaedic conditions and to allow the investigator to proceed further in articles referred to in the bibliography. If this book is used for students in school, explanatory lectures should be used to supplement it. The bibliography is quite general and complete and offers opportunity for further intensive study of any subject.

A F V

Textbook of Diagnostic Roentgenology By LEWIS J FRIEDMAN, M D 623 pages,
17 × 25 cm D Appleton-Century Co, New York 1937 Price, \$10 00

This volume attempts to cover the whole field of diagnostic roentgenology and hence deals with each aspect in too brief a fashion to serve the purpose of the man specializing in that field. It is perhaps best suited to give the physician in general practice a survey of the whole subject.

The viewpoint is consistently maintained that the roentgenologist is a medical consultant and should be in possession of all available clinical data before rendering his opinion.

W L K

Carcinoma of the Female Genital Organs By M C MALINOWSKY, and E QUATER
Translated from the Russian by A S Schwartzmann, A B., M D 255 pages,
15.5 × 23.5 cm Bruce Humphries, Inc, Boston 1936 Price, \$5 00

This work is a rather superficial one covering all phases of carcinoma of the female sexual organs. It is contributed to by eleven different authors, and contains much interesting statistical data compiled chiefly from the European clinics and from the works of outstanding European investigators. It is interesting to note throughout this work the similarity of the treatment of these types of carcinoma in Europe and in this country. It is surprising, however, that no mention is made of the use of spinal alcohol injections in the treatment of pelvic pain in far advanced cases.

The chapter on the "Clinical Picture of Carcinoma of the Uterus" by Dr Quater, and the one on "Metastatic Carcinoma of the Ovaries" by Dr Pojarissky are particularly good. The last chapter in the book deals with carcinoma of the female sexual organs from the viewpoint of disability and social insurance. The illustrations throughout the book, especially the microphotographs, are quite poor.

This work would be much more valuable if it were more exhaustive.

J C D

COLLEGE NEWS NOTES

NOMINATIONS, 1938-39

Elective Offices

Dr William J Kerr, President-Elect, San Francisco, Calif, accedes to the Presidency

New Nominations

President-Elect	O H Perry Pepper, Philadelphia, Pa
First Vice-President	James B Herrick, Chicago, Ill
Second Vice-President	Noble Wiley Jones, Portland, Oregon
Third Vice-President	Charles T Stone, Galveston, Tex

Respectfully submitted,

Committee on Nominations,
JONATHAN C MEAKINS, *Chairman*

NOTICE OF AMENDMENT TO THE BY-LAWS

In accordance with the present By-Laws of the American College of Physicians and by direction of the Board of Regents at a regular meeting held on April 18, 1937, notice is hereby given to the Fellows and Masters of the College that the following amendment to the By-Laws has been approved by said Board of Regents and will be presented for adoption or rejection at the Annual Business Meeting to be held in New York City April 7, 1938

(An addition to the By-Laws, Article IV, Section 1, to be added as an additional paragraph)

"Any member of the Board of Governors unable to attend the Annual Session shall appoint as his alternate, with all the privileges of a Governor, a Master or Fellow of his district who will be in attendance at that Session Upon presentation to the Chairman of the Board of Governors of a certificate of appointment, the alternate shall be recognized and act in the full capacity of Governor for the Session to which he has been appointed The same alternate shall not be appointed for more than two consecutive years "

NEW LIFE MEMBERS

The following Fellows have been entered, upon their subscriptions, as Life Members of the American College of Physicians, at the dates indicated, making a total of ninety-four

Dr Louis H Fligman, Helena, Mont, January 10, 1938
Dr Max H Weinberg, Pittsburgh, Pa, January 13, 1938
Dr W P Anderton, New York, N Y, January 13, 1938
Dr Orrin Sage Wightman, New York, N Y, January 15, 1938
Dr J Dorwin Mabey, Montclair, N J, January 15, 1938
Dr Robert L Levy, New York, N Y, January 15, 1938
Dr Harry S Emery, Portland, Maine, January 17, 1938
Dr Alex M Burgess, Providence, R I, January 18, 1938

- Dr Theodore S Bacon, Springfield, Mass, January 19, 1938
 Dr Mary Riggs Noble, Bowmansdale, Pa, January 24, 1938
 Dr Mary Elizabeth Bass, New Orleans, La, January 24, 1938
 Dr Karl Vogel, New York, N Y, January 25, 1938

GIFTS TO THE COLLEGE LIBRARY

Grateful acknowledgment is made of the receipt of the following donations to the College Library of publications by members

Books

- Dr Linn J Boyd (Fellow), New York, N Y—"A Study of the Simile in Medicine",
 Dr Thomas Hall Shastid (Fellow), Duluth, Minn—"Tramping to Failure" and "How to Stop War-Time Profiteering",
 Dr William D Stroud (Fellow), Philadelphia, Pa, co-author with Dr Lawrason Brown (Fellow, deceased), Dr George R Minot (Fellow), Dr William B Castle (Fellow), Dr George B Eusterman (Fellow) and Dr George F Dick—an autographed copy of each of the 1934, 1935 and 1936 "Year Book of General Medicine",
 Dr Russell M Wilder (Fellow), Rochester, Minn—an autographed copy of "A Primer for Diabetic Patients",
 Dr Lowell S Selling (Associate), Detroit, Mich—"Diagnostic Criminology"

Reprints

- Major Joseph R Darnall (Fellow), (MC), U S A—2 reprints,
 Dr Ralph M Fellows (Fellow), Osawatomie, Kan—2 reprints,
 Lt Col Arthur R Gaines (Fellow), (MC), U S A—1 reprint,
 Dr Paul John Hanzlik (Fellow), San Francisco, Calif—51 reprints,
 Dr Edward G Huber (Fellow), Boston, Mass—1 reprint,
 Dr George Morris Lewis (Fellow), New York, N Y—25 reprints,
 Dr James L McCartney (Fellow), Catskill, N Y—1 reprint,
 Dr Joseph A Pollia (Fellow), Los Angeles, Calif—14 reprints,
 Dr Thomas Hall Shastid (Fellow), Duluth, Minn—2 reprints,
 Dr Virgil E Simpson (Fellow), Louisville, Ky—1 reprint,
 Dr Walter M Simpson (Fellow), Dayton, Ohio—3 reprints,
 Dr Wilham L Smith (Fellow), New Orleans, La—1 reprint,
 Dr Felix Cunha (Associate), San Francisco, Calif—10 reprints,
 Dr Herbert R Edwards (Associate), New York, N Y—4 reprints,
 Dr Hyman I Goldstein (Associate), Camden, N J—1 reprint,
 Dr John M Nicklas (Associate), Valhalla, N Y—2 reprints,
 Dr Lowell S Selling (Associate), Detroit, Mich—18 reprints

Dr C W Waddell (Fellow), Fairmont, W Va, has contributed two original copies of the "Annals of Medicine," Volume I, Nos 1 and 2, to the permanent archives of the College These were the first two journals sponsored and published by the College

Grateful acknowledgment is also made of the receipt of the following gifts

- Mr and Mrs James Inglis, Ann Arbor, Mich—1 book, "The Collapse Therapy of Pulmonary Tuberculosis" by John Alexander, M D

Metropolitan Life Insurance Company, New York, N Y—1 book, "Twenty-Five Years of Health Progress, A Study of the Mortality Experience Among the Industrial Policyholders of the Metropolitan Life Insurance Company, 1911 to 1935"

SECTIONAL MEETING OF ARKANSAS MEMBERS

Dr Oliver C Melson (Fellow and Governor for Arkansas) reports that the Fellows and Associates of the American College of Physicians of Arkansas met at the Albert Pike Hotel in Little Rock on November 8 Dr John H Musser (Fellow), New Orleans, was the guest speaker Those present included Dr H T Smith of McGehee, Dr F N Gordon of Fayetteville, Dr George B Fletcher, Dr A G Sullivan and Dr Euclid Smith of Hot Springs, Dr Charles T Chamberlain of Fort Smith, Dr L D Massey of Osceola, Dr J D Riley of State Sanatorium, Dr A A Blair of Fort Smith, Dr J N Compton, Dr John R Dibrell and Dr Oliver C Melson of Little Rock

Such state meetings will be inaugurated as a yearly feature in Arkansas

Dr John G Young (Fellow), Dallas, Tex, is President of the Texas Pediatric Society and of the Dallas Pediatric Society Dr Young is also Consultant to the Dallas Tuberculosis Association and Chief of the Medical Staff of Freeman Memorial Clinic for Children

Dr Howard S Brasted (Fellow), Hornell, N Y, addressed the Pre-Medic Club of Houghton College recently on "Blood Transfusions and Blood Typing"

Dr J W Torbett, Sr (Fellow), Marlin, Texas, gave a lecture on "Undulant Fever of the Chronic Types" before the Brown-Mills and San Saba County Medical Society meeting in November Dr Torbett is director and one of the founders of the Marlin Hot Wells Foundation, which recently established the Crippled Children's Hospital and Hot Water Pool in Marlin, Texas

Dr E W Gehring (Fellow and Governor for Maine), having recently resigned as Chief of Medical Service of Maine General Hospital at Portland, has been succeeded by Dr E H Drake (Fellow)

Dr B S Pollak (Fellow) is the medical director of the new Hudson County Tuberculosis Hospital and Sanatorium, newest unit of the Jersey City Medical Center This hospital, towering some eighteen or twenty stories, will accommodate 510 patients In equipment, furniture and facilities, nothing has been spared to make the institution one of the most complete in the country

At the Annual Congress of the Council on Medical Education and Hospitals of the American Medical Association, to be held in Chicago, February 14 and 15, 1938, the following Fellows of the College will participate

- Dr Willard C Rappleye, Dean of Columbia University College of Physicians and Surgeons, New York City, "The Functions of the Special Examining Boards",
- Dr Burrell O Raulston, Professor of Medicine, University of Southern California School of Medicine, Los Angeles, "An Introduction to Clinical Medicine and Some Variations in the Curriculum of the Third and Fourth Years in Medical School",
- Dr J G FitzGerald, Director of the School of Hygiene and Connaught Laboratories, University of Toronto, Toronto, Ont, Canada, "Medical Student Instruction in Preventive Medicine",
- Dr John H Musser, Professor of Medicine, Tulane University of Louisiana School of Medicine, New Orleans, and Dr James D Bruce, Director of the Department of Postgraduate Medicine, University of Michigan, Ann Arbor, participants in the Symposium on Graduate Medical Education
-

Dr Herbert L Bryans (Fellow), Pensacola, Fla, has been elected President of the Gulf Coast Clinical Society

The Bronx Hospital of New York City sponsored a series of afternoon lectures for physicians during November and December Dr Alvan L Barach (Fellow), New York City, presented an address on "Peripheral Circulatory Failure and Acute Pulmonary Edema Occurring as Complications in Pneumonia", Dr Elliott P Joslin (Fellow), Boston, "Diabetes Mellitus", and Dr Russell L Cecil (Fellow), New York City, "Chronic Arthritis"

Dr Samuel M Bittinger (Fellow) has been appointed assistant superintendent and medical director of the new sanatorium for the treatment of tuberculosis at Black Mountain, N C

The Commonwealth Fund of New York has approved a grant of \$10,857 annually for three years to Western Reserve University School of Medicine, Cleveland, especially for research on chronic nephritis by Dr Joseph M Hayman (Fellow), who is associate professor of medicine

At the last annual meeting of the Medical Society of the State of Pennsylvania, the Board of Trustees and the past presidents presented to Dr Walter F Donaldson (Fellow), Pittsburgh, Secretary of the Society for many years, an oil portrait of himself Dr Arthur C Morgan (Fellow), Philadelphia, made the presentation address

Dr William Egbert Robertson (Fellow), Philadelphia, presented an address, "Dr Rush and the Signers of the Constitution," before the Philadelphia County Medical Society on the occasion of the marking of the one hundred and fiftieth anniversary of the signing of the Constitution of the United States

Dr Charles S Holbrook (Fellow), New Orleans, has been elected President-Elect of the Southern Psychiatric Association

Dr Priscilla White (Fellow), Boston, addressed the fifth annual scientific meeting of the Georgia Pediatric Society at Atlanta on December 9 on "Endocrine Problems in Juvenile Diabetes, Recent Problems in Juvenile Diabetes"

Dr George G Onstein (Fellow), New York City, delivered a paper on "The Pathogenesis of Pulmonary Tuberculosis from the Physician's Point of View" in connection with the fall graduate conferences of the Wayne County (Michigan) Medical Society, the Detroit Department of Health and the Detroit Tuberculosis Sanatorium

Dr Irving S Wright (Fellow), New York City, was a guest speaker at the annual "Scientific Day" of Montefiore Hospital, Pittsburgh, recently, his address being on "A Critical Analysis of Recent Advances in the Study of Vascular Disease"

Dr David P Barr (Fellow), St Louis, Dr Russell L Cecil (Fellow), New York City, Dr Alfred Friedlander (Fellow), Cincinnati, Dr Ernest E Irons (Fellow), Chicago, and Dr Roger I Lee (Fellow), Boston, are members of the Advisory Committee on Pneumonia Control, recently appointed by Dr Thomas Parran (Fellow), Surgeon General of the U S Public Health Service

Dr Charles C Bass (Fellow), Dean of Tulane University of Louisiana School of Medicine, delivered the principal address at the recent dedication of the Rudolph Matas Medical Library, which is the library of Tulane University of Louisiana School of Medicine, named in honor of Dr Rudolph Matas, Emeritus Professor of Surgery at the University

Dr Henry A Christian (Fellow), Boston, Mass, was one of the speakers at the dedication of the new building of the Syracuse University College of Medicine, Syracuse, N Y, on November 22

Dr Clarence E de la Chapelle (Fellow), New York City, is acting chairman of the Department of Medicine of the New York University College of Medicine

Dr James Edward Hubbard (Associate), is the director of the Huntington (W Va) Radium and X-Ray Clinic, which recently opened new quarters in the Memorial Hospital at Huntington

Dr Lee Rice (Fellow), San Antonio, Texas, has been elected a vice-president of the Southern Medical Association

Among speakers from the United States on the seventh cruise congress of the Pan American Medical Association, which left New York City January 15 were the following

- Dr Edwin C Ernst (Fellow), St Louis, "Recent Developments in Relation to the Radiation Management of Cancer",
Dr Howard R Hartman (Fellow), Rochester, Minn, "Treatment of Hemorrhagic Ulcer of Stomach or Duodenum",
Dr Herman N Bundesen (Fellow), Chicago, Ill, "Amebiasis"
-

The Section on the Medical Sciences of the American Association for the Advancement of Science devoted its entire program, December 27 to January 1, to a symposium on syphilis. The following were contributors

- Dr John A Kolmer (Fellow), Philadelphia, "Serologic Reactions in Relation to Infection and Treatment of Syphilis",
Dr Paul A O'Leary (Fellow), Rochester, Minn, "Neurosyphilis",
Dr Walter M Simpson (Fellow), Dayton, Ohio, "High Temperatures",
Dr Dudley C Smith (Fellow), University, Va, "Untoward Reactions—Intercurrent Infections",
Dr Thomas Parran (Fellow), Washington, D C, "Syphilis A Public Health Program"
-

Dr Solomon Strouse (Fellow), formerly of Chicago, has been appointed Associate Clinical Professor of Medicine at the University of Southern California Medical School at Los Angeles

As a recognition of his medical and public health services to Cuba, the Order of Merit of Carlos Finlay was recently conferred upon Dr Edgar Mayer (Fellow), New York City

Dr C C Carpenter (Fellow), Dean of the Wake Forest Medical School, will be the director of the new school of medical technology, recently announced by Wake Forest College and the Rex Hospital, of Raleigh, N C

Dr O H Perry Pepper (Fellow), Philadelphia, was a guest speaker and guest clinician on the program of the William Moore Guilford Clinic, a newly organized graduate clinic day, observed by the Good Samaritan Hospital, Lebanon, Pa, and the Lebanon County Medical Society, each year during the week of Dr Guilford's birthday. Dr Guilford reached the age of 105 years on November 26, 1937

Dr C Lydon Harrell (Fellow), Norfolk, will serve as medical adviser of the new Tidewater Victory Memorial Hospital for the treatment of tuberculosis near Norfolk

Dr Herbert Z Giffin (Fellow), Professor of Medicine in the University of Minnesota Graduate School of Medicine, has been elected President of the Staff of the Mayo Clinic

Dr G Harlan Wells (Fellow), Philadelphia, has been elected President of the Homeopathic Medical Society of Pennsylvania

OBITUARIES

DR LAWRASON BROWN

Dr Lawrason Brown (Fellow) died at his home in Saranac Lake, December 26, 1937, at the age of sixty-six. He had been ill at periods for the past several years with symptoms traceable to longstanding pulmonary tuberculosis. Mrs. Brown survives him.

Dr. Brown was born in Baltimore, September 29, 1871, and there received his education. Johns Hopkins gave him the A. B. degree in 1895, and the M. D. in 1900. He soon went to Saranac Lake where he came under the influence of Trudeau. Assuming the duties of resident physician at the Trudeau Sanatorium in 1901, his great energy, efficiency and intelligence were released to build on the foundation which Trudeau had labored to lay. With zeal that grew from the spirit of truth within him and thrived in the atmosphere of humaneness about him, Brown perfected the plan of treatment of tuberculous patients in the sanatorium, organized the records, instituted a follow-up system which in later years yielded rich clinical studies, and furthered scientific study in the laboratory and clinic. He soon became a leader among that remarkable group of physicians who made Saranac Lake a fountain head of knowledge of tuberculosis and established a standard of clinical practice which was the pattern for the country. The national antituberculosis campaign was gaining momentum and, as a part of this, the need for sanatoria became more and more apparent, largely on account of what was being demonstrated at the Trudeau Sanatorium. As these were established throughout the country, Brown's influence spread afar. He conceived the idea of organizing physicians engaged in sanatorium work, and this fructified in the creation of the American Sanatorium Association, now grown to be the most important society of its kind in the country. He established and edited the *Journal of the Outdoor Life*, bringing to tuberculous patients the essential facts of hygiene and proclaiming the creed of acquiescence and hope which is a vital part of the "cure." For thousands of these patients his "Rules for Recovery from Tuberculosis" was and still is a lamp in the darkness. An unfailing scientific curiosity constantly renewed his energy which he spent freely in discussions with his confreres at informal and formal meetings, in teaching, and in writing numerous articles for periodicals, books and systems of medicine, as well as longer monographs. It was his habit always to keep testing and retesting medical principles, mostly in the light of the Trudeau follow-up system and its revelation of the ultimate fate of his former patients, the result of which was a progressive refinement of the understanding of the behavior of tuberculosis and its diagnosis and treatment. The soundness of his understanding, the honesty of his thinking, and the quality of his leadership won for Brown a degree of respect and distinction enjoyed by few in their chosen medical fields. His long experience and deep knowledge enabled

him to evaluate better than most physicians the factors which aid the healing of tuberculosis, and among these he always assigned a high place to the *vis medicatrix naturae*. He deprecated ignorance of the possibilities of rest treatment and the fallacy of attempting to displace it completely with "collapse" therapy, though he did not underrate the latter. Rather, he exemplified that discriminating judgment in selecting a plan of treatment for the individual patient which marks the seasoned clinician.

At the time of his death, Dr. Brown was consultant to the Trudeau Sanatorium and the Waverly Hills Sanatorium, Louisville, Ky., also a trustee of the Trudeau Sanatorium, the New York State Hospital at Ray Brook, and the Potts Memorial Hospital, Livingston, N. Y., and a member of the advisory council of the Henry Phipps Institute, Philadelphia. He had been president of the American Sanatorium Association, American Clinical and Climatological Association, and the National Tuberculosis Association. He was a fellow and life member of the American College of Physicians, and a member of the Association of American Physicians, the American Association of Thoracic Surgery, and of other organizations. He received the Trudeau medal from the National Tuberculosis Association in 1933. He was awarded the honorary degree of doctor of science from Dartmouth College in 1931 and from the Medical College of Virginia in 1936.

Lawrason Brown had the devotion of his patients, the respect of his professional brethren, and the love of his friends.

J. BURNS AMBERSON, JR., M.D., F.A.C.P.

DR. JOHN LEE

Dr. John Lee of Detroit died September 22, 1937, after a long illness.

Dr. Lee was born in Detroit in 1869, and graduated from the Detroit College of Medicine in 1890. For many years he taught as Assistant Professor of Medicine at his alma mater, his active clinical teaching being done at St. Mary's Hospital, where he served throughout his long professional career as Attending Physician in the Department of Medicine. Dr. Lee served during the Spanish American War. He had been an Associate of the American College of Physicians for many years.

From the time that he started in practice, Dr. Lee devoted a large part of his time to teaching in the wards at St. Mary's Hospital, as well as carrying on a large practice. Energetic and enthusiastic, he enjoyed the warm friendship and respect of the many physicians who owed their clinical training to him during their college careers.

HENRY R. CARSTENS, M.D., F.A.C.P.,
Governor for Michigan

DR ALBERT WARREN FERRIS

Dr Albert Warren Ferris (Fellow), East Orange, N J, died October 4, 1937, following a prolonged illness of encephalitis with a parkinsonian syndrome, at the age of 81

Dr Ferris was born in Brooklyn, N Y, 1856, attended Adelphi Academy of Brooklyn, Newark Academy, Newark Latin School and Hasbronck Institute of Jersey City, A B, New York University, 1878, A M, same, 1885, M D, Columbia University College of Physicians and Surgeons, 1882, interned at Kings County Hospital, Flatbush, L I, 1883-85, assistant and later resident physician, Sanford Hall for Insane, Flushing, N Y, 1885-91, physician-in-charge, Dr Choate's Home for Insane, Pleasantville, N Y, 1906-07, senior resident physician, Glen Springs Sanitarium, Watkins, N Y, 1912-13 and from 1917 to 1930, president, New York State Commission on Lunacy, 1907-11 (appointed by former Governor Charles E Hughes), medical expert and director, Saratoga Springs State Reservation Commission, 1913-16, for some time consulting physician to the Binghamton State and Manhattan State (N Y) hospitals, also during his earlier career, Assistant in Neurology, Vanderbilt Clinic, Columbia University, 1893-1900, member, Phi Beta Kappa and Delta Upsilon fraternities (national first vice president of latter in 1884 and in 1902), member and ex-vice president, ex-editor of journal and a delegate to the American Medical Association from the Medical Society of the State of New York, Fellow and ex-chairman of a section, New York Academy of Medicine, member, American Psychiatric Association, Fellow, American Medical Association, member of various New York county medical societies, according to his residence at the time, author of many articles in national medical journals and of over 250 articles appearing in the International Encyclopedia and in the International Year Book, Fellow of the American College of Physicians since 1920

Dr Ferris is survived by a brother, Mr Richard Ferris, New York City
Seldom does one see more evidence of a fruitful professional life His career was an honor to the medical profession and to the College

CLARENCE L ANDREWS, M D, F A C P,

Governor for New Jersey

DR E MARK HOUGHTON

Dr E Mark Houghton of Detroit, Michigan, died December 12, 1937

Born in 1867, he was educated at the University of Michigan, where he received his Ph C degree in 1893, and M D in 1894 After further work in pharmacology, he joined the staff of Parke, Davis and Company in 1895, where he became director of medical research and biological laboratories He held this position until 1929, when he was made consulting director

Besides membership in the Wayne County Medical Society, Detroit

Medical Club, Michigan State Medical Society, and American Medical Association, he held membership in the Society of American Bacteriologists, American Pharmaceutical Association, Society of Immunologists, National Tuberculosis Association, and in 1910 was a delegate to the United States Pharmacopoeia Convention. Dr. Houghton had been a Fellow of the American College of Physicians since 1921.

Enjoying a high reputation for work in his professional field, Dr. Houghton was also a genial friend to his many professional colleagues. A scholarly gentleman, he will be greatly missed by his many friends both in the profession and the laity.

HENRY R. CARSTENS, M.D., F.A.C.P.,
Governor for Michigan

DR. HARVEY ELIJAH WELLMAN

On October 20, 1937, Dr. Harvey E. Wellman died at the Jane Brown Memorial Hospital at Providence as the result of an acute duodenitis and enteritis of eight days' duration.

Dr. Wellman, a Fellow of the College (1937), had earned the deep respect and affection of his colleagues and of the patients who had come under his care. Always an earnest and capable clinician, a most conscientious worker in his various hospital assignments, he found time for an interest in the broader aspects of medical study and always had a keen eye for the improvement of the service in the various hospital organizations with which he was connected. During his term as Resident Physician at the Rhode Island Hospital he was particularly interested in the Pathological Laboratory and as a result of his efforts a radical improvement in this department took place. As Assistant Physician in the Division of University Health at Brown University he won the confidence and affection of the student body. During the last few years of his life he became especially interested in diseases of the chest and his place in the Thoracic Clinics of the Charles V. Chapin and Rhode Island Hospitals will be hard to fill.

At the time of his death Dr. Wellman was forty-five years old. He was graduated from Williams College with the degree of A.B. in 1914 and from Harvard Medical School in 1926. He served with the U.S. Navy Base Hospital No. 4 during the World War. He was appointed Assistant Visiting Physician to the Rhode Island Hospital in 1936, Visiting Physician to the Charles V. Chapin Hospital in 1935 and Consulting Physician to the Rhode Island State Infirmary in 1935. He was a diplomate of the National Board of Medical Examiners, the author of a number of published papers and a member of the following organizations: Providence Medical Association, Rhode Island Medical Society, New England Heart Association and American Medical Association.

ALEX. M. BURGESS, M.D., F.A.C.P.,
Governor for Rhode Island

DR HENRY WILLIAM JAEGER

Dr Henry William Jaeger (Associate, 1928), born March 14, 1888, at Washington, D C, died October 21, 1937, at his home in Washington of coronary occlusion

Dr Jaeger was educated in the Public Schools of Washington and at the George Washington University, from which he was graduated in medicine in 1911. He served internships at Casualty Hospital, Washington, and at the German Hospital, Brooklyn, N Y. He was a member of the Medical Society of the District of Columbia, a Fellow of the American Medical Association, and an Associate of the American College of Physicians.

Dr Jaeger was particularly interested in music and was a member of the choir of the Nobles of the Mystic Shrine. During the last years of his life he was tenor soloist at the Washington Cathedral. He had those "mysterious motions of the soul, not to be defined save in strange melodies." Because of its illusiveness, its subtle shades, and its vanishing ecstasies, he found music entrancing.

Keeping abreast of the advances in medicine, Dr Jaeger had a lucrative practice. His patients became his friends, because he had a capacity for a deep and sustained friendship, which he manifested not only when occasion offered, but he sought opportunities to extend to others those little amenities which are precious to all of us. He was admired and loved not only for loyalty to friendship, but also for his integrity of purpose and the sweetness of his nature, and because he was of the company of those who make the barren places fruitful with kindness.

Furnished by courtesy of The Medical Society
of the District of Columbia

DR THOMAS TIPTON WALKER

In the death of Thomas Tipton Walker, the medical profession loses a well qualified pathologist, a keen student of medicine, and one particularly suited to research. He proudly and meticulously followed the precepts of medical ethics and demanded of himself and his colleagues a very high standard of work and achievement. Six published papers attest his scientific interest in medicine. In his hours of recreation, he made the same demands of himself as in his work—to excel in whatever he did.

Dr Walker was born in Atlanta, Georgia, March 11, 1904. He graduated from Emory University in 1924 with the degree of Bachelor of Science, cum laude, and the following year received his Master's degree from the University of North Carolina. He then entered Harvard Medical College and in 1928 a scholarship took him to London, where he worked at St Thomas' Hospital under Sir Cuthbert Wallace.

On graduation from Harvard Medical College, he accepted a residency

in pathology at the Boston City Hospital, and during his stay there he instructed in physiology and pathology at Tufts Medical School until 1931. After postgraduate study abroad at Eppendorfer Krankenhaus and in Frankfurt at the Stadische Krankenhaus, he returned to the United States and accepted a position as pathologist at the Duke Hospital, Durham, North Carolina. While at Durham he was instructor in pathology at Duke University. In 1932 he became director of the Department of Laboratories at the House of the Good Samaritan and Mercy Hospitals, Watertown, New York, later being appointed consulting pathologist at the Jefferson County Sanatorium at Watertown. These positions he fulfilled most efficiently and rendered to Watertown and surrounding communities the highest type of pathological service.

He was diplomate of the National Board of Medical Examiners and also of the American Board of Pathology, a member and officer of the Jefferson County Medical Society, a member of the New York State Medical Society, the American Medical Association, the Association of Pathologists and Bacteriologists, American Society of Clinical Pathologists, the New York State Association of Public Health Laboratories, the Pathological Society of Eastern New York, and an Associate of the American College of Physicians since April 28, 1935.

Dr. Walker died November 13, 1937, and in his untimely death medicine was deprived of a research student who was well qualified to be a leader in the advance of medical science.

He is survived by his widow, Lillie Cutlar Walker.

This obituary was very kindly prepared by Walter S. Atkinson, M.D., of Watertown, New York.

C. F. TENNEY, M.D., F.A.C.P.,
Governor for Eastern New York, New York

PROGRAM
TWENTY-SECOND ANNUAL SESSION
AMERICAN COLLEGE OF PHYSICIANS
NEW YORK, N Y

April 4-8, 1938

GENERAL SESSIONS AND LECTURES

James H Means, President

NEW YORK EXECUTIVE COMMITTEE

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James Ralph Scott, Vice-Chairman

Edward R Loveland, Executive Secretary

Robert A Cooke

Peter Irving

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William W Herrick

Thomas T Mackie

COMMITTEE ON ENTERTAINMENT

Howard F Shattuck, Chairman

George C Andrews

Robert L Levy

F Warner Bishop

Kenneth R McAlpin

Louis F Bishop, Jr

Edgar Stillman

Ralph H Boots

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COMMITTEE ON TRANSPORTATION AND HOTELS

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 Mrs Russell L Cecil Mrs Howard F Shattuck
 Mrs Archibald Douglas, Jr Mrs Edgar Stillman
 Mrs Francis P Garvan Mrs Kenneth Taylor
 Mrs Lucius Wilmerding

GENERAL INFORMATION

New York Headquarters
 Waldorf-Astoria Hotel, 50th St & Park Ave

The Waldorf-Astoria Hotel will be headquarters for Officers, Regents, Governors and members of the College, also the General Headquarters for registration, technical exhibits, general scientific sessions, special lectures and round table luncheon-conferences

List of New York Hotels (partial)	Blocks from Head- quarters	Rates per day	
		Single Room with bath	Double Room with bath
WALDORF-ASTORIA, 50th St & Park Ave		\$5 00 and up	\$8 00 and up
Barclay, 111 E 48th St	1	5 00 and up	8 00 and up
Belmont Plaza, 49th St & Lexington Ave	$\frac{1}{4}$	3 00 and up	5 00 and up
Biltmore, 43d St & Madison Ave	6	4 00 and up	7 00 and up
Commodore, 42d St & Lexington Ave	7	3 50 and up	5 00 and up
Lexington, 48th St & Lexington Ave	$\frac{1}{4}$	4 00 and up	6 00 and up
Murray Hill, 41st St & Park Ave	9	4 00 and up	{ 3 50 inside room 5 00 outside room
Pennsylvania, 34th St & 7th Ave	20	3 50 and up	5 00 and up
Prince George, 14 E 28th St	22	2 25 to 4 00	3 50 to 6 00
Roosevelt, 45th St & Madison Ave	5	5 00 and up	7 00 and up
Shelton, 49th St & Lexington Ave	$\frac{1}{4}$	3 50 and up	4 50 and up

Members should make reservations directly with hotels of their choice. Mention the convention of the American College of Physicians, for rates above quoted are, in many instances, only for this occasion.

WHO MAY REGISTER—

- (a) All members of the American College of Physicians in good standing for 1938 (dues, if not paid previously, may be paid at the Registration Bureau)
- (b) All newly elected members

- (c) House Officers of the hospitals participating in the program, without registration fee, upon presentation of proper identification, exhibits, general sessions and afternoon lectures
- (d) Members of the Medical Corps of Public Services of the United States and Canada, without registration fee, upon presentation of proper credentials
- (e) Qualified physicians who may wish to attend this Session as visitors. Such physicians shall pay a registration fee of \$12 00, and shall be entitled to one year's subscription to the ANNALS OF INTERNAL MEDICINE (in which the proceedings will be published), included within such fee

REGISTRATION BLANKS FOR ALL CLINICS AND DEMONSTRATIONS AND ROUND TABLE CONFERENCES will be sent with the formal program to members of the College. Guests will secure registration blanks at the Registration Bureau during the Session.

TRANSPORTATION—On account of nationwide reductions in railroad fares, there are no convention rates any longer in effect. In many instances, however, reduced round trip tickets are in effect from certain localities. Members should consult their local ticket agents.

The Committee on Transportation will issue full data concerning local transportation at the meeting.

THE GENERAL BUSINESS MEETING OF THE COLLEGE will be held at 11 30 a m, Thursday, April 7, immediately following the general scientific program of the morning. All Masters and Fellows of the College are urged to be present.

There will be the election of Officers, Regents and Governors, the reports of the Treasurer and of the Executive Secretary, the presentation of an amendment to the By-Laws, and the induction to office of the new President, Dr. William J. Kerr, San Francisco, Calif.

BOARD AND COMMITTEE MEETINGS—The following meetings are scheduled as indicated. Special meetings will be announced and posted.

A *special dinner* will be tendered to the Board of Regents by members of the Board of Governors at the Waldorf-Astoria Hotel, Sunday evening, April 3.

COMMITTEE ON CREDENTIALS

Sunday, April 3, 9 00 a m Carpenter Suite, Fourth Floor, Waldorf-Astoria Hotel

BOARD OF REGENTS

Carpenter Suite, Fourth Floor, Waldorf-Astoria Hotel

Sunday, April 3, 2 30 p m

Tuesday, April 5, 12 00 m *

Friday, April 8, 12 00 m *

BOARD OF GOVERNORS

Carpenter Suite, Fourth Floor, Waldorf-Astoria Hotel

Monday, April 4, 5 00 p m

Wednesday, April 6, 12 00 m *

* Buffet luncheon served

SPECIAL FEATURES

MONDAY, APRIL 4, 1938

THE ANNUAL SMOKER will be held in the Ballroom of the Waldorf-Astoria Hotel on Monday, immediately following the evening meeting, at about ten-twenty o'clock. It will be limited to men only. The entertainment will consist of a floor show to be followed by informal singing by the audience. Light refreshments and beer will be served. Fellows and Associates are invited to attend the Smoker as guests of the College.

TUESDAY, APRIL 5, 1938

THEATER NIGHT. Blocks of desirable seats for some of the most popular plays have been reserved. These will be on sale at the Waldorf Ticket Agency, and those desiring to go to the theater are urged to buy their tickets promptly after registering for the Session.

-- -- WEDNESDAY, APRIL 6, 1938

CONVOCATION OF THE COLLEGE—8 30 p m, Grand Ballroom, Waldorf-Astoria Hotel. All Masters and Fellows of the College and those to be received in Fellowship should be present. Newly elected Fellows who have not yet been received in Fellowship are requested to assemble in the West Foyer of the Waldorf-Astoria Hotel (third floor, adjoining west side of the Ballroom) at 7 45 o'clock, preparatory to the formation of the procession. They will occupy especially reserved seats in the central section of the Ballroom, to which they will be conducted by the Convocation marshal promptly at 8 30. It is customary for all to appear in evening dress.

The Convocation is open to all physicians and their families generally. A cordial invitation is also issued to such of the general public as may be interested.

Following the Convocation Ceremony, the President will present the John Phillips Memorial Medal for 1937-38, and will thereafter deliver the Presidential Address. Dr. Karl T. Compton, President of the Massachusetts Institute of Technology, Cambridge, Mass., will deliver the Convocational Oration, "Possibilities in Biological Engineering."

The Presidential Reception, with dancing, will follow immediately after the program in the Grand Ballroom.

THURSDAY, APRIL 7, 1938

THE ANNUAL BANQUET OF THE COLLEGE will be held in the Grand Ballroom of the Waldorf-Astoria Hotel on Thursday evening at eight o'clock. Dr. James Alexander Miller, General Chairman of the Twenty-second Annual Session of the College, will be the Toastmaster. The address of the evening, "Education in a Changing World," will be delivered by Honorable John H. Finley, LL.D., Associate Editor of the New York Times. Dr. Finley is a well known author and educator, having formerly been Professor of Politics at Princeton University, President of the College of the City of New York and Exchange Harvard Professor to the Sorbonne.

All members of the College, physicians of New York and visitors attending the Session, with their families, are cordially invited. Tickets should be purchased at the Registration Bureau by Wednesday afternoon.

PROGRAM OF ENTERTAINMENT FOR VISITING WOMEN

The Headquarters of the Women's Entertainment Committee will be located in the Empire Room at the Waldorf-Astoria Hotel. Each visitor will receive a program of the activities planned for their entertainment by the Women's Entertainment Committee. A special secretary will be in charge to assist visitors in arranging their entertainment program. Visiting women are requested to register here on arrival and make reservations for the events announced in the program. Additional literature containing information regarding theaters, restaurants, night clubs and other places of entertainment will be available at the registration desk.

The sole purpose of the Women's Entertainment Committee is to assist the visiting women in securing the greatest possible enjoyment and entertainment from their visit to New York. It is hoped that as a result of the activities of this Committee visitors will carry away with them pleasant memories of their stay.

It would greatly facilitate the work of the Committee if each Fellow or Associate who will be attended by ladies will return the card accompanying the program as promptly as possible.

MONDAY, APRIL 4, 1938

Afternoon Registration, Empire Room, Waldorf-Astoria Hotel

Evening 8 15 p m, Reception in Empire Room

9 00 p m, Evening performance at Radio City Music Hall. Feature picture and stage show, including the famous Rockettes.

TUESDAY, APRIL 5, 1938

Morning Free for shopping, etc.

Afternoon 12 30 p m, Luncheon and fashion show in the Empire Room. Tickets, \$2 00.

Evening Theater, optional.

WEDNESDAY, APRIL 6, 1938

Morning Free.

Afternoon 2 30 p m, Visit to the Frick Museum and Metropolitan Museum of Art. Buses leave the Waldorf-Astoria at 2 30 p m. Fare, \$1 00.

5 00 p m, Tea at the Junior League Club House as guests of the Women's Committee.

Evening 8 30 p m, Convocation and dance at the Waldorf-Astoria.

THURSDAY, APRIL 7, 1938

Morning 11 15 a m, Tour of Radio City, including the Museum of Science and Industry, Sky Gardens, Broadcasting Studios, etc. Tickets, \$1 50. Tour ends at 4 00 p m. Luncheon may be had in restaurants in Radio City.

Evening 8 00 p m, Annual Banquet of the College, Waldorf-Astoria.

THE NEW YORK ACADEMY OF MEDICINE at 2 East 103rd Street (on Fifth Avenue) will be open to the members of the American College of Physicians and the participants in its Sessions in New York City.

The Library of the Academy of Medicine is open daily from 9 00 a m to 10 30 p m. The Medical Library is the second largest in the United States, being excelled only by that of the Surgeon General's Library in Washington. The rare books and the Library's incunabula are particularly noteworthy.

The services of the Committee on Medical Education will be available to the members of the American College of Physicians and to all other visiting physicians for information relative to hospitals and clinics throughout the City of New York. The Committee also publishes a daily schedule and bulletin of medical and surgical meetings, lectures, conferences and rounds, as well as a daily list of major surgery in the city's hospitals, open to physicians.

On Friday evening, April 8, at eight-thirty o'clock, Dr. Thomas M. Rivers of the Rockefeller Institute will deliver the Biggs Memorial Lecture at the Academy upon the subject, "The Twentieth Century Version of the De Novo Origin of Infectious Agents, and its Significance in the Control of Disease." All members of the College who remain in New York that evening are cordially invited to attend this meeting.

THE AMERICAN MUSEUM OF NATURAL HISTORY at 77th Street from Columbus Avenue to Central Park West is open every day in the year—week-days, including holidays, from 9 00 a m to 5 00 p m, and Sundays from 1 00 p m to 5 00 p m. There is no charge for admission, excepting to the Planetarium.

The Museum is an institution devoted to the study of the earth and the life existing on it, step by step over a period estimated to be over five hundred million years, from the lowest form to man. Here the fruits of more than half a century of scientific discovery, painstaking research, extensive exploration and courageous pioneering appear in the form of exhibits which reconstruct much of the history of the earth and the mighty animals that once roamed its surface. In the Museum's halls you will find thousands of natural history exhibits from virtually every section of the globe, aside from the special exhibits in the Roosevelt Memorial and the Hayden Planetarium.

THE EXPOSITION AND TECHNICAL EXHIBIT will be located on the Third Floor of the Waldorf-Astoria Hotel.

By official action of the Board of Regents of the College, the Technical Exhibits will be raised to a higher level of excellence through the elimination of all irrelevant and non-scientific entries. The rules adopted, governing this and future Exhibits, are as follows:

- (1) Exhibitors shall be admitted on invitation only,
- (2) The initial approved "Invitation List" shall be made up by the Committee and the Executive Secretary. Both the firm and the product must be approved. Preference shall be given to exhibits of a scientific nature, such as pharmaceuticals, equipment and medical books,
- (3) Additions to the initial approved "Invitation List" may be made by the Committee after application by firms, with the requirement that they submit complete literature concerning their products and their organization,
- (4) The "Invitation List" may be revised annually on the recommendation of the Committee.

The Committee on Exhibits has thoughtfully investigated each exhibit before extending invitations. The number of exhibitors has been reduced, and it is hoped that the members and visiting physicians will find the exhibits more interesting and more beneficial. The exhibits will be particularly representative of the interests of Internal Medicine and its allied specialties, and will include medical literature, pharmaceutical products, apparatus and appliances, specialized physicians' furniture and many other items of special interest. The educational value of these exhibits adds greatly to the interesting features of the meeting. Each doctor is urged to visit each of the booths, for he will certainly find something new and scientifically valuable. Special intermissions in the general program have been arranged, providing additional time for the inspection of exhibits.

LIST OF EXHIBITORS

The following exhibitors have been approved for admission to the Exhibit

	<i>Space</i>
Adlanco X-Ray Corporation, New York, N Y	47-48
Allergia Products Co, Newton, Mass	28
Allison Company, W D, Indianapolis, Ind	53
American Hospital Supply Corporation, Chicago, Ill	15
Appleton-Century Company, D, New York N Y	24
Arlington Chemical Company, The, Yonkers N Y	2
Austin, Nichols & Co, Inc, Brooklyn, N Y	37
Ayerst, McKenna & Harrison (United States) Limited, Montreal, Que	9
Baum Co, Inc, W A, New York, N Y	55
Becton, Dickinson & Co, Rutherford N J	72-73
Bilhuber-Knoll Corp, Jersey City, N J	25
Cambridge Instrument Co, Inc, New York, N Y	61
Cameron Surgical Specialty Company, Chicago, Ill	21-59
Chappel Laboratories, Rockford Ill	14
Collins, Inc, Warren E, Boston, Mass	54
Davies, Rose & Company, Limited, Boston, Mass	7
Davis Company, F A, Philadelphia, Pa	30
Doak Company, The, Cleveland, Ohio	16
Fougera and Co, Inc, E, New York N Y	26
General Electric X-Ray Corporation, Chicago, Ill	33-34
Gerber Products Company, Fremont, Mich	40
Glen Springs, The, Watkins Glen, N Y	45
Gradwohl School of Laboratory Technique, St Louis Mo	32
Hamilton Manufacturing Co, Two Rivers, Wis	41-42
Hoeber, Inc, Paul B, New York, N Y	27
Hoffmann-La Roche, Inc, Nutley, N J	44
Jones Metabolism Equipment Co, Chicago Ill	6
Kalak Water Co, New York, N Y	4
LaMotte Chemical Products Company, Baltimore, Md	58
Lea & Febiger, Philadelphia, Pa	20
Lederle Laboratories, Inc, New York, N Y	10-11-12
Lippincott Company, J B, Philadelphia, Pa	1
Macmillan Company, The, New York, N Y	60
Maltine Company, The, New York, N Y	74
Mead Johnson & Company, Inc, Evansville, Ind	22
Medical Bureau, The, Chicago, Ill	17
Medical Case History Bureau, New York, N Y	69
Merck & Co Inc, Rahway, N J	18-19
Merrell Company, The Wm S, Cincinnati, Ohio	68
Mosby Company, The C V, St Louis Mo	29
Muller Laboratories, The, Baltimore, Md	56
Nelson & Sons, Thomas, New York, N Y	5
New York Medical Exchange, The, New York, N Y	3
Oxford University Press, New York N Y	8
Oxygen Therapy Service, Inc, New York, N Y	57
Patch Company, The E L, Boston, Mass	23
Petrolagui Laboratories, Inc, Chicago, Ill	70
Picker X-Ray Corporation, New York, N Y	35
Ralston Purina Co, St Louis, Mo	31
Rare Chemicals, Inc, Nepera Park, N Y	66-67

Sanborn Company, Cambridge, Mass	51
Sandoz Chemical Works, Inc., New York, N Y	65
Saunders Company, W B, Philadelphia, Pa	75
Schering Corporation, Bloomfield, N J	52
Searle & Company, G D, Chicago, Ill	43
Smith, Kline & French Laboratories, Philadelphia, Pa	49-50
Spicer and Company, Glendale, Calif	39
Squibb & Sons, E R, New York, N Y	71
Stearns & Company, Frederick, Detroit, Mich	64
Taylor Instrument Companies, Rochester, N Y	62-63
Vegev, Incorporated, New York, N Y	46
White Laboratories Incorporated, Newark, N J	13
Winthrop Chemical Company, Inc., New York, N Y	76-77

GENERAL SESSIONS

The object of the General Sessions portion of our program is to provide opportunity for the physicians who constitute our membership, and their guests, to hear statements by competent authorities on topics of lively interest in the fields of internal medicine, the basic sciences, related specialties and other fields in which knowledge gained will better fit the physician to serve the public and practice his profession.

The attempt has been made to provide a diversified and well balanced program. Reports of new and original work are included as well as reviews of important subjects. The desires of the membership as to both topics and speakers have been obtained insofar as this can be done by questionnaire, and heeded in the formation of the program.

In the belief that it is not incumbent upon the physician "to stick to his last" in a meeting of his College, if by that is meant that nothing but purely scientific medicine should be permitted to consider, certain items touching upon *social*, *public* and possibly even *philosophical aspects* of medicine, as well as the more usual ones on diagnosis and treatment, have been included.

GENERAL SESSIONS PROGRAM

Ballroom, Waldorf-Astoria Hotel, New York, N Y

FIRST GENERAL SESSION

Monday Afternoon, April 4, 1938

Presiding Officer

James Alexander Miller, New York, N Y

p m

2 30 Addresses of Welcome

James Alexander Miller, General Chairman of the Twenty-Second Annual Session, and President of the New York Academy of Medicine

Clarence G Bandler, President of the New York County Medical Society

Willard C Rappleye, Dean, College of Physicians and Surgeons, Columbia University

Hon Fiorello H LaGuardia, Mayor of the City of New York

Response to Addresses of Welcome

James H Means, President of the American College of Physicians

OUTLINE OF SESSION

TIME	MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY
9 00 a m to 12 00 m	Morning free Registration, Exhibits, etc	3d General Session	4th General Session	5th General Session	6th General Session
12 30 p m to 2 00 p m	Luncheon	Round Table Luncheons	Round Table Luncheons	Round Table Luncheons	Round Table Luncheons
2 30 p m to 5 00 p m	1st General Session	1st Clinical Session	2d Clinical Session	3d Clinical Session	4th Clinical Session
5 00 p m to 8 00 p m	Dinner	Dinner	Dinner		
8 00 p m to 10 00 p m	2d General Session followed by Smoker	Open	Convocation, followed by President's Reception	ANNUAL BANQUET	
					2 30-4 30 4th Lecture Program

- 3 15 Trends in Public Health
Thomas Parran, Surgeon-General, U S Public Health Service, Washington, D C
- 3 45 INTERMISSION
- 4 15 The Social Responsibilities of Medicine
John P Peters, John Slade Ely Professor of Medicine, Yale University School of Medicine, New Haven, Conn (By invitation)
- 4 45 A Broader View of Postmortem Examinations
Alan Gregg, Director for Medical Sciences of the Rockefeller Foundation, New York, N Y (By invitation)
- 5 15 ADJOURNMENT

SECOND GENERAL SESSION

Monday Evening, April 4, 1938

Presiding Officer

William J Kerr, San Francisco, Calif

- p m
- 8 00 The Mechanism of Heat Loss and Temperature Regulation
Eugene F Du Bois, Professor of Medicine, Cornell University Medical College, Medical Director, Russell Sage Institute of Pathology, Physician-in-Chief, New York Hospital, New York, N Y
- 8 20 Some Desirable Supplements to the Present Trends in Medical Investigation
Roger I Lee, Fellow, Harvard University, and Consultant in Internal Medicine, Boston, Mass
- 8 40 Certain Limitations of Preventive Medicine
Henry A Christian, Hersey Professor of the Theory and Practice of Physic, Harvard University Medical School, Physician-in-Chief, Peter Bent Brigham Hospital, Boston, Mass
- 9 00 Clinical and Experimental Observations on Focal Infection
Russell L Cecil, Professor of Clinical Medicine, Cornell University Medical College, New York, N Y, and
D Murray Angevine, Instructor in Pathology, Cornell University Medical College, New York, N Y (By invitation)
- 9 20 The Ageing Process as a Medical-Social Problem
George Morris Piersol, Professor of Medicine, University of Pennsylvania Graduate School of Medicine, Physician-in-Chief, Abington Memorial Hospital, Physician, University of Pennsylvania Graduate Hospital, Philadelphia, Pa, and
Edward L Bortz, Associate Professor of Medicine, University of Pennsylvania Graduate School of Medicine, Chief of Medical Service B, The Lankenau Hospital, Philadelphia, Pa
- 9 40 Nutritional Deficiency Disease
George R Minot, Professor of Medicine, Harvard University Medical School Director, Thorndike Memorial Laboratory, Boston City Hospital, Boston, Mass
- 10 00 ADJOURNMENT

10 20 o'Clock

SMOKER

Ballroom, Waldorf-Astoria Hotel

An interesting and amusing program has been arranged Admission by
registration badge Men only

THIRD GENERAL SESSION

Tuesday Morning, April 5, 1938

Presiding Officer

James E. Paullin, Atlanta, Ga

a m

- 9 00 Experimental Heart Disease
George Edward Hall, Associate Professor, Department of Medical Research, University of Toronto, Toronto, Ont., Canada (By invitation)
- 9 20 Concerning the Association of Bronchial Asthma and Left Ventricular Failure and the Possible Ill Effects from the Use of Epinephrine, unless the Latter can be Excluded
Fred M. Smith, Professor and Head of Department of Theory and Practice of Medicine, State University of Iowa College of Medicine, Physician-in-Chief, University Hospitals, Iowa City, Iowa
- 9 40 Further Comments on Coronary Thrombosis
James B. Herrick, Emeritus Professor of Medicine, Rush Medical College, Chicago, Ill
- 10 00 Obesity and Hypertension Clinical and Experimental Observations
J. Edwin Wood, Jr., Professor of the Practice of Medicine, University of Virginia Department of Medicine, University, Va., and
James R. Cash, Professor of Pathology, University of Virginia Department of Medicine, University, Va. (By invitation)
- 10 15 Climate, Mode of Life, and Heart Disease
Paul D. White, Physician, Massachusetts General Hospital, Lecturer in Medicine, Harvard University Medical School, Boston, Mass
- 10 30 INTERMISSION
- 11 00 Physiologic Effects of Operation (Bilateral Resection of Splanchnic Nerves and First and Second Lumbar Ganglia) for Essential Hypertension
Edgar V. Allen, Associate Professor of Medicine, University of Minnesota (Mayo Foundation), Head of Section in Division of Medicine, Mayo Clinic, Rochester, Minn., and
A. W. Adson, Professor of Neurosurgery, University of Minnesota (Mayo Foundation), Head of Section on Neurosurgery, Mayo Clinic, Rochester, Minn. (By invitation)
- 11 20 Prophylaxis in Allergy
Richard A. Kern, Professor of Clinical Medicine, University of Pennsylvania School of Medicine and Graduate School of Medicine, Chief of Allergy Section and Chief of Outpatient Department, Hospital of the University of Pennsylvania, Philadelphia, Pa

- 11 40 Physiological Methods in the Diagnosis and Treatment of Asthma and Emphysema (Moving Picture Demonstration)
 Alan L. Barach, Assistant Professor of Clinical Medicine, Columbia University College of Physicians and Surgeons, New York, N. Y.
- 12 00 ADJOURNMENT
-

FOURTH GENERAL SESSION

Wednesday Morning, April 6, 1938

Presiding Officer

G. Gill Richards, Salt Lake City, Utah

a m

- 9 00 Chronic Brucellosis (Undulant Fever) An Analytical Study of the Positive Reactors among School Children
 Fred E. Angle and William H. Algie, Department of Medicine, University of Kansas Hospitals, Attending Physicians to Bethany Methodist Hospital, Providence Hospital and St. Margaret's Hospital, Kansas City, Kan.
- 9 15 Prognosis and Treatment of Erysipelas
 John A. Toomey, Associate Professor of Pediatrics, Western Reserve University School of Medicine, Cleveland, Ohio
- 9 35 The Value of Antitoxin in Scarlet Fever
 Francis G. Blake, Sterling Professor of Medicine, Yale University School of Medicine, Physician-in-Chief, New Haven Hospital, New Haven, Conn.
- 9 50 Factors Influencing the Incidence and Course of Otitis Media in Scarlet Fever
 Conrad Wesselhoef, Associate Professor of Theory and Practice, Boston University School of Medicine, Associate in Communicable Diseases (Department of Pediatrics and School of Public Health), Harvard University Medical School, Boston, Mass.
- 10 10 The Present Status of Methods for the Prophylaxis of Acute Anterior Polomyelitis
 John A. Kolmer, Professor of Medicine, Temple University School of Medicine, Director of the Research Institute of Cutaneous Medicine, Philadelphia, Pa.
- 10 30 INTERMISSION
- 11 00 Observations on the Clinical Aspects, Complications and Treatment of Acute Upper Respiratory Tract Infections
 Arlie V. Bock, Henry K. Oliver Professor of Hygiene, Harvard University, Physician, Massachusetts General Hospital, Boston, Mass. (By invitation)
- 11 15 The Affective Disorders in Medical Practice
 Thomas P. Sprunt, Associate in Medicine, Johns Hopkins University School of Medicine, Associate Professor of Medicine, University of Maryland School of Medicine, Baltimore, Md.
- 11 30 Experimental Observations on the Treatment of Hypertension
 Harry Goldblatt, Professor of Experimental Pathology and Associate Director of the Institute of Pathology, Western Reserve University School of Medicine, Cleveland, Ohio (By invitation)

- 11 50 Experiences with Insulins of Prolonged Activity in Ambulatory Patients
 H Clare Shepardson, Associate Clinical Professor of Medicine, University of California Medical School, San Francisco, Calif, and
 Richard D Friedlander, Instructor in Medicine, University of California Medical School, San Francisco, Calif (By invitation)
- 12 00 ADJOURNMENT

ANNUAL CONVOCATION

Wednesday Evening, April 6, 1938

8 30 o'Clock

Grand Ballroom, Waldorf-Astoria Hotel

All members of the profession and the general public are cordially invited No special admission tickets will be required

- 1 Address by the President of the College
 James Howard Means
- 2 Presentation of newly-elected Fellows and recital of the Pledge
 George Morris Piersol, *Secretary General*
- 3 Presentation of John Phillips Memorial Medal for 1937-38
- 4 Announcement of Research Fellow of the College for 1938
- 5 Convocational Oration "Possibilities in Biological Engineering"
 Karl T Compton, President, Massachusetts Institute of Technology, Cambridge, Mass

President's Reception

The Reception and Dance will follow immediately after the program Newly-inducted Fellows should sign the Roster and secure their Fellowship Certificates during the Reception

FIFTH GENERAL SESSION

Thursday Morning, April 7, 1938

Presiding Officer

William D Stroud, Philadelphia, Pa

a m

- 9 00 The Clinical Significance of Punctate Basophilia in the Erythrocyte
 Ernest H Falconer, Clinical Professor of Medicine, University of California Medical School, San Francisco, Calif
- 9 15 Macrocytic Anemias, other than Pernicious Anemia, Associated with Lesions of the Gastrointestinal Tract
 Cyrus C Sturgis, Professor of Internal Medicine, University of Michigan Medical School, Director, Thomas Henry Simpson Memorial Institute for Medical Research, Director, Department of Internal Medicine, University Hospital, Ann Arbor, Mich
- 9 35 Clinical and Hematological Review of Sprue based on the Study of 150 Cases
 Ramon M Suárez, Associate Clinical Professor of Tropical Medicine, School of Tropical Medicine of Puerto Rico, San Juan, P R

- 9 55 The Challenge of Appendicitis
Reginald Fitz, Wade Professor of Medicine, Boston University School of
Medicine, Director, Evans Memorial, Boston, Mass
- 10 15 Correlation of Clinical and Laboratory Data in Diseases of Lymph Nodes
Raphael Isaacs, Associate Professor of Medicine, University of Michigan
Medical School, Assistant Director, Thomas Henry Simpson Mem-
orial Institute for Medical Research, Ann Arbor, Mich
- 10 30 INTERMISSION
- 11 00 Concerning the Acquired Resistance of Fixed Tissue Cells to Injury
(Lantern slides)
William de B MacNider, Kenan Research Professor of Pharmacology,
and Dean University of North Carolina School of Medicine, Chapel
Hill, N C
- 11 30 ADJOURNMENT, to be followed by

ANNUAL BUSINESS MEETING

The Annual Business Meeting of the College will be held immediately after the last paper All Masters and Fellows are urged to be present An amendment to the By-Laws of the College is to be presented for consideration and adoption Official reports from the Treasurer and Executive Secretary will be read, new Officers, Regents and Governors will be elected, and the President-Elect, Dr William J Kerr, will be inducted into office

Thursday Evening, 8 00 o'Clock

Ballroom, Waldorf-Astoria Hotel

THE ANNUAL BANQUET OF THE COLLEGE

(Procure Tickets at the Registration Bureau)

Consult Special Banquet Program

Toastmaster James Alexander Miller, New York, N Y

Address of the Evening "Education in a Changing World" Hon John H Finley,
LL D, Associate Editor of the New York Times

SIXTH GENERAL SESSION

Friday Morning, April 8, 1938

Presiding Officer

James D Bruce, Ann Arbor, Mich

a m

- 9 00 A Differential Classification of the Various Types of Colitis Their Manage-
ment

J Arnold Bargen, Associate Professor of Medicine, University of Min-
nesota (Mayo Foundation), Consultant in Medicine, Mayo Clinic,
Rochester, Minn

- 9 15 Hypoglycemia Following Encephalitis

Jonathan C Meakins, Professor of Medicine and Director of Department,
McGill University Faculty of Medicine, Physician-in-Chief, Royal
Victoria Hospital, Montreal, Que, Canada

- 9 30 Basal Metabolism The Practical Significance of the "Variability" as Distinguished from the "Constancy" of the Basal Metabolic Rate in Individuals and in Various Groups of Diseases
Walter M Boothby, Professor of Experimental Metabolism, University of Minnesota (Mayo Foundation), Head of Section for Metabolic Investigation, Mayo Clinic, Rochester, Minn
- 9 50 Studies on the Pathologic Physiology of the Exophthalmos of Graves' Disease
David Marine, Assistant Professor of Pathology, Columbia University College of Physicians and Surgeons, Director of Laboratories, Montefiore Hospital, New York, N Y
- 10 10 Experiences in Treating Exophthalmic Goiter in a Large Municipal Hospital
Willard O Thompson, Associate Clinical Professor of Medicine, Rush Medical College, Research Associate in Pathology, Cook County Hospital, Chicago, Ill ,
S G Taylor, III, Clinical Associate in Medicine, Rush Medical College, Chicago, Ill (By invitation),
Karl A Meyer, Associate Professor of Surgery, Northwestern University Medical School, Attending Surgeon and Medical Superintendent, Cook County Hospital, Chicago, Ill (By invitation),
R W McNealy, Associate Professor of Surgery, Northwestern University Medical School, Attending Surgeon, Cook County Hospital, Chicago, Ill (By invitation)
- 10 30 INTERMISSION
- 11 00 Cevitamic Acid A Critical Analysis of Its Use in Clinical Medicine
Irving S Wright, Assistant Professor of Clinical Medicine, Columbia University, New York, N Y
- 11 20 Common Gastrointestinal Emergencies Their Early Recognition and Treatment
George B Eusterman, Professor of Medicine, University of Minnesota (Mayo Foundation), Head of Section on Medicine, Mayo Clinic, Rochester, Minn
- 11 40 Acute Disseminated Lupus Erythematosus—a Systemic Disease
Edward Rose, Assistant Professor of Clinical Medicine, University of Pennsylvania School of Medicine, Philadelphia, Pa , and
Donald M Pillsbury, Assistant Professor of Dermatology and Syphilology, University of Pennsylvania School of Medicine, Philadelphia, Pa (By invitation)
- 12 00 ADJOURNMENT

PROGRAM OF AFTERNOON LECTURES

This course of Afternoon Lectures is a feature of the program arranged at the request of a large number of members. The course is presented as an elective, as a whole or for individual days, in place of hospital clinics. The lectures will not conflict with the General Sessions or with the Round Table Luncheon-Conferences. The lectures will be presented daily, Tuesday to Friday, inclusive, from 2 30 to 4 30 p m , in the Ballroom of the Waldorf-Astoria Hotel.

This year the attempt has been made to devote most of the lectures to problems in therapeutics. The newer drugs such as sulphanilamide, physical therapy, oxygen therapy and psychotherapy will be presented, and also papers on treatment of disturbances of sodium metabolism and of such diseases as hypertension and disorders of the liver.

The lectures will be open to all members and guests of the College.
Admission by regular registration badge

Tuesday Afternoon, April 5, 1938

BALLROOM, WALDORF-ASTORIA HOTEL

Presiding Officer

Chauncey Warring Dowden, Louisville, Ky

p m

- 2 30 Therapeutics of Liver Disease
Albert M Snell, Associate Professor of Medicine, University of Minnesota (Mayo Foundation), Head of a Section on Medicine, Mayo Clinic, Rochester, Minn, and
Jesse L Bollman, Associate Professor of Experimental Pathology, University of Minnesota (Mayo Foundation), Associate in Division of Experimental Surgery and Pathology, Mayo Clinic, Rochester, Minn (By invitation)
- 3 30 Recent Advances in the Use of Drugs for Treatment of Bacterial Infections
Eli Kennerly Marshall, Jr, Professor of Pharmacology and Experimental Therapeutics, The Johns Hopkins University School of Medicine, Baltimore, Md (By invitation)
- 4 30 ADJOURNMENT
-

Wednesday Afternoon, April 6, 1938

BALLROOM WALDORF-ASTORIA HOTEL

Presiding Officer

T Homei Coffen, Portland, Oregon

p m

- 2 30 Recent Advances in the Therapeutic Use of Drugs Whose Action Simulates Sympathetic and Parasympathetic Nervous Activity
Isaac Starr, Hartzell Professor of Research Therapeutics, University of Pennsylvania School of Medicine, Philadelphia, Pa (By invitation)
- 3 30 A Critical Survey of Physical Therapy Technic
Stafford L Warren, Associate Professor of Medicine in Charge of Division of Radiology of the University of Rochester, School of Medicine and Dentistry, and Strong Memorial Hospital, Rochester, N Y (By invitation)
- 4 30 ADJOURNMENT
-

Thursday Afternoon, April 7, 1938

BALLROOM, WALDORF-ASTORIA HOTEL

Presiding Officer

Edward Leo Tuohy, Duluth, Minn

p m

- 2 30 Treatment of Disturbances of Sodium Metabolism
Dana W Atchley, Associate Professor of Medicine, Columbia University College of Physicians and Surgeons, New York, N Y (By invitation)

- 3 10 Sensitization Tests—Then What?
George L. Waldbott, Detroit, Mich
- 3 50 The Emergency Treatment of Dangerous Hypertension
Albert S. Hyman, Director, Within Foundation for the Study and Prevention of Heart Disease, New York, N. Y.
- 4 05 Typhus Fever (Brill's Disease) A Study of 271 Cases
Simon Rusefeld Blatteis, Clinical Professor of Medicine, New York University College of Medicine Professor of Clinical Medicine, Long Island College of Medicine, Brooklyn, N. Y.
- 4 30 ADJOURNMENT

Friday Afternoon, April 8 1938

BALLROOM, WALDORF-ASTORIA HOTEL

Presiding Officer

Edwin Wagner Gehring, Portland, Maine

- p m
- 2 30 Psychotherapy, with Special Reference to the Use of Hypnosis
James L. McCartney, Psychiatrist, New York State Vocational Hospital, Catskill, N. Y.
- 3 30 Oxygen Therapy
Alex M. Burgess, Chairman of Division of University Assistant Professor of Biology, Brown University, Columbia Chief, Charles V. Chapin Hospital, Visiting Physician Hospital, Providence, R. I.
- 4 30 ADJOURNMENT

Minnesota Mayo Clinic,

ROUND TABLES

The Round Tables proved so popular at the St. Louis meeting, university of been made a special feature of the New York program. They will outstanding authorities on the subjects assigned.

All Round Tables are held at the Waldorf-Astoria Hotel, and all Syphilology, meetings. The groups will meet around the luncheon table beginning at 12 30 p m and terminating promptly at 2 00 p m. Being held at Philadelphia, Pa. will be no conflict with the General Sessions in the forenoon and the afternoon.

Admission to these discussions will, of necessity, be limited capacity of the rooms in which they are held. There are rooms with arranged at the for luncheon varying from 75 to 200 persons. A total of 625 can be elective, as a each day. This means a total capacity of 2,500 persons for the sessions will not provide accommodations for at least one Round Table Luncheon. References. The of the College attending the Convention. Admission is by ticket of 10 to 4 30 p m, \$1.75 each, which includes the cost of the luncheon, city and foreign gratuities.

In order to insure reservations for the Round Tables, it will es to problems make application promptly when the application forms are received. therapy, oxygen program later. When the application is made it is suggested that treatment of dis- submit in writing any question or phase of the subject which he wishes to discuss. These requests will be considered by the Leaders of the Round Tables with disorders of such subjects as seem most in demand.

ROUND TABLE LUNCHEON-CONFERENCES

Room	Le Perroquet Suite	Jansen Suite Dining Room	Jansen Suite Salon	Assembly Rooms M to R	West Foyer
Capacity	150	75	100	100	200
Tuesday April 5	I DIABETES Russell M Wilder Leader	II SYPHILIS Thomas Parran Leader	III TUBERCULOSIS Gerald B Webb Leader	IV GASTRO- ENTEROLOGY T Grier Miller Leader	V CARDIOLOGY Paul D White Leader
Wednesday April 6	VI ALLERGY Robert A Cooke Leader	VII VASCULAR DISEASE Eugene M Lyndis Leader	VIII NUTRITION William P Murphy Leader	IX PSYCHONEUROSES Austen Fox Riggs Leader	X ENDOCRINOLOGY David P Barr Leader
Thursday April 7	XI PNEUMONIA Russell L Cecil Leader	XII ARTHRITIS Ralph H Boots Leader	XIII CARDIOLOGY Robert L Levy Leader	XIV DIABETES H O Mosenthal Leader	XV DISEASES OF THE BLOOD George R Minot Leader
Friday April 8	XVI ALLERGY Francis M Raekemann Leader	XVII TUBERCULOSIS J Burns Amberson, Jr Leader	XVIII GASTRO- ENTEROLOGY George B Lusterman Leader	XIX DISEASES OF THE BLOOD Cyrus C Sturgis Leader	XX VIRUS DISEASES Thomas Francis, Jr Leader

PROGRAM OF ROUND TABLES

Tuesday, April 5, 1938

WALDORF-ASTORIA HOTEL

Le Perroquet Suite, Fourth Floor

(Capacity, 150)

I

12 30-2 00 p m ROUND TABLE on Diabetes Mellitus

Leader Russell M Wilder, Professor and Chief of Department of Medicine,
University of Minnesota (Mayo Foundation), Consulting Physician, Mayo
Clinic, Rochester, Minn

WALDORF-ASTORIA HOTEL

Jansen Suite Dining Room, Fourth Floor

(Capacity, 75)

II

12 30-2 00 p m ROUND TABLE on Syphilis

Leader Thomas Parran, Surgeon-General, United States Public Health
Service, Washington, D C

WALDORF-ASTORIA HOTEL

Jansen Suite Salon, Fourth Floor

(Capacity, 100)

III

12 30-2 00 p m ROUND TABLE on Tuberculosis

Leader Gerald B Webb, Consulting Physician, Sunnyrest Sanatorium,
Glockner Sanatorium and Hospital, National Methodist Episcopal Sana-
torium for Tuberculosis and St Francis Hospital and Sanatorium,
President, Colorado Foundation for Research in Tuberculosis, Colorado
Springs, Colo

WALDORF-ASTORIA HOTEL

Assembly Rooms M to R, Fourth Floor

(Capacity, 100)

IV

12 30-2 00 p m ROUND TABLE on Gastro-Enterology

Leader T Grier Miller, Professor of Clinical Medicine, University of Penn-
sylvania School of Medicine, Chief of Gastrointestinal Section, Hospital
of the University of Pennsylvania, Philadelphia, Pa

WALDORF-ASTORIA HOTEL

West Foyer, Third Floor

(Capacity, 200)

V

12 30-2 00 p m ROUND TABLE on Cardiology

Leader Paul D White, Physician, Massachusetts General Hospital, Lecturer
in Medicine, Harvard University Medical School, Boston, Mass

Wednesday, April 6, 1938

WALDORF-ASTORIA HOTEL

Le Perioquet Suite, Fourth Floor

(Capacity, 150)

VI

12 30-2 00 p m ROUND TABLE on Diseases of Allergy

Leader Robert A Cooke, Assistant Professor of Clinical Medicine, Cornell
University Medical College, Special Consultant in Allergy and Director
of Department of Allergy, Roosevelt Hospital, New York, N Y

WALDORF-ASTORIA HOTEL

Jansen Suite Dining Room, Fourth Floor

(Capacity, 75)

VII

12 30-2 00 p m ROUND TABLE on Vascular Disease

Leader Eugene M Landis, Assistant Professor of Medicine and Research
Associate in Pharmacology, University of Pennsylvania School of Medi-
cine, Philadelphia, Pa

WALDORF-ASTORIA HOTEL

Jansen Suite Salon, Fourth Floor

(Capacity, 100)

VIII

12 30-2 00 p m ROUND TABLE on Disorders of Nutrition

Leader William P Murphy, Associate in Medicine, Harvard University Medi-
cal School, Senior Associate in Medicine, Peter Bent Brigham Hospital,
Boston, Mass

WALDORF-ASTORIA HOTEL

Assembly Rooms M to R, Fourth Floor

(Capacity, 100)

IX

12 30-2 00 p m ROUND TABLE on Psychoneuroses

Leader Austen Fox Riggs, Clinical Professor of Neurology, Columbia Uni-

versity College of Physicians and Surgeons, Medical Director and President of Austen Riggs Foundation, Stockbridge, Mass

WALDORF-ASTORIA HOTEL

West Foyer, Third Floor

(Capacity, 200)

X

12 30-2 00 p m ROUND TABLE on Endocrinology

Leader David P Barr, Professor of Medicine, Washington University School of Medicine, Physician-in-Chief, Barnes Hospital, St Louis, Mo

Thursday, April 7, 1938

WALDORF-ASTORIA HOTEL

Le Perroquet Suite, Fourth Floor

(Capacity, 150)

XI

12 30-2 00 p m ROUND TABLE on Pneumonia

Leader Russell L Cecil, Professor of Clinical Medicine, Cornell University Medical College, Associate Visiting Physician, New York Hospital, New York, N Y

WALDORF-ASTORIA HOTEL

Jansen Suite Dining Room, Fourth Floor

(Capacity, 75)

XII

12 30-2 00 p m ROUND TABLE on Arthritis

Leader Ralph H Boots, Associate in Medicine, Columbia University College of Physicians and Surgeons, Assistant Attending Physician and Physician to Arthritis Clinic, Presbyterian Hospital, New York, N Y

WALDORF-ASTORIA HOTEL

Jansen Suite Salon, Fourth Floor

(Capacity, 100)

XIII

12 30-2 00 p m ROUND TABLE on Cardiology

Leader Robert L Levy, Professor of Clinical Medicine, Columbia University College of Physicians and Surgeons, Associate Visiting Physician and Cardiologist, Presbyterian Hospital, New York, N Y

WALDORF-ASTORIA HOTEL

Assembly Rooms M to R, Fourth Floor

(Capacity, 100)

XIV

12 30-2 00 p m ROUND TABLE on Diabetes Mellitus

Leader H O Mosenthal, Professor of Medicine, New York Post-Graduate Medical School, Columbia University, Attending Physician, New York Post-Graduate Hospital, New York, N Y

WALDORF-ASTORIA HOTEL

West Foyer, Third Floor

(Capacity, 200)

XV

12 30-2 00 p m ROUND TABLE on Diseases of the Blood

Leader George R Minot, Professor of Medicine, Harvard University Medical School, Director, Thorndike Memorial Laboratory, Boston City Hospital, Boston, Mass

Friday, April 8, 1938

WALDORF-ASTORIA HOTEL

Le Perroquet Suite, Fourth Floor

(Capacity, 150)

XVI

12 30-2 00 p m ROUND TABLE on Diseases of Allergy

Leader Francis M Rackemann, Associate in Medicine, Harvard University Medical School, Physician and Chief of Medical Department, Massachusetts General Hospital, Boston, Mass

WALDORF-ASTORIA HOTEL

Jansen Suite Dining Room, Fourth Floor

(Capacity, 75)

XVII

12 30-2 00 p m ROUND TABLE on Tuberculosis

Leader J Burns Amberson, Jr, Professor of Clinical Medicine, Columbia University College of Physicians and Surgeons and New York University College of Medicine, Visiting Physician, Tuberculosis Service, Bellevue Hospital, New York, N Y

WALDORF-ASTORIA HOTEL

Jansen Suite Salon, Fourth Floor

(Capacity, 100)

XVIII

12 30-2 00 p m ROUND TABLE on Gastro-enterology

Leader George B Eusterman, Professor of Medicine, University of Minnesota (Mayo Foundation), Head of Section on Medicine, Mayo Clinic, Rochester, Minn

WALDORF-ASTORIA HOTEL

Assembly Rooms M to R, Fourth Floor

(Capacity, 100)

XIX

12 30-2 00 p m ROUND TABLE on Diseases of the Blood

Leader Cyrus C Sturgis, Professor of Internal Medicine, University of Michigan Medical School, Director, Thomas Henry Simpson Memorial Institute for Medical Research, Director, Department of Internal Medicine, University Hospital, Ann Arbor, Mich

WALDORF-ASTORIA HOTEL

West Foyer, Third Floor

(Capacity, 200)

XX

12 30-2 00 p m ROUND TABLE on Virus Diseases

Leader Thomas Francis, Jr, Member of the Staff of the International Health Division of the Rockefeller Foundation, New York, N Y

PROGRAM OF CLINICS AND SPECIAL DEMONSTRATIONS

The Program for the Clinical Sessions has been completed, and, following an old New York custom, clinics will be held in the afternoon instead of in the morning

There will be three separate clinics on each of the four days at Bellevue, New York and Presbyterian Hospitals At Mount Sinai there will be two programs each day The Department of Health is giving one clinic on each of the four days The Hospital of the Rockefeller Institute is giving two programs during the week and the following hospitals are each offering one program on one afternoon Roosevelt, St Luke's, Long Island College and Post-Graduate

All these clinics are to be patient-clinics, not lectures, and special effort has been made to have each clinic a sort of symposium dealing with the clinical phases of some one particular branch of medicine such as cardiac, vitamin, endocrine, renal or blood diseases As a matter of fact, all the fields of medicine seem to be fairly well covered in the programs outlined

Stress has also been laid on the Clinical Pathological Conferences and one or more of these will be found on each of the afternoons Some of the clinics belong

in the group of general medicine in which the run-of-the-ward cases will be presented and discussed by the attending staff. This makes it possible to do away with the ward walks which had to be limited to very small groups.

The clinics to be given by the Department of Health draw the material from their very large clinics on syphilis and gonorrhea and deal with these important subjects, not only from the standpoint of diagnosis and therapy, but also from their public health and preventive aspects.

Of course, it has not been possible to utilize all of the vast facilities that New York affords nor to avail ourselves of the opportunities that were offered by many of the other hospitals and institutions in the city. It did not seem wise to provide seating capacity in excess of that demanded by the College for such sessions, the clinics as offered will accommodate 2,500 individuals daily.

Clinic Sessions will begin promptly at 2:30 o'clock in the afternoon. *Everyone who wishes to attend a clinic must secure a ticket, for the collection of tickets will be rigidly enforced.*

There will also be a few special demonstrations for relatively small groups. Those who are interested will have an opportunity to see Dr. Barach's oxygen and helium apparatus in practical use at the Presbyterian Hospital where Dr. Francis Carter Wood will also demonstrate the high voltage (1,000,000 volts) x-ray machine recently installed in the hospital.

At Mount Sinai Hospital Dr. Robert Frank will demonstrate his method of assaying sex hormones, and Dr. Reuben Ottenberg and his associates will demonstrate technical methods for studying liver function.

At Bellevue Dr. Howard Fox will have a small clinic for the demonstration of some especially interesting cases of cutaneous syphilis and Dr. Lucy Sutton will exhibit apparatus for fever therapy in children.

At New York Hospital Dr. Henry Richardson and his associates will give a special demonstration on various aspects of bronchiectasis and Dr. Eugene Du Bois will show his new metabolism unit for research purposes.

It will be noted that many of these demonstrations occupy only a relatively small portion of the time allotted to clinic sessions in an afternoon. It has been arranged that Fellows desiring to attend these short demonstrations may attend any of the other clinics that are in progress at the same hospital during the remainder of the afternoon, either before or after the demonstration. In this way they will not sacrifice an entire afternoon for a relatively short demonstration.

The Committee responsible for the assembling of these clinics has received the cordial cooperation of the staffs in the hospitals contributing and trusts that the program will meet with the hearty approval of the Fellows of the College.

NEW YORK CITY AS A MEDICAL CENTER

HISTORICAL RETROSPECT

DR JAMES J WALSH, author of "The History of Medicine in New York State," is authority for the statement that the history of medicine began when the first permanent colonists located at Fort Orange in 1625. There arrived two "consolers of the sick," Bastiaen Jansen Crol and Jan Huyck, who also conducted religious services until the arrival of the first ordained minister in 1628. In 1633 a second minister arrived, accompanied by a schoolmaster. Both added to the medical resources, for it was the duty of the schoolmaster to assist the dominie as consoler of the sick as well as to serve as the teacher of youth.

Any retrospect of medicine in New York would require frequent references to the contributions made to the subject by Dr. Walsh, and fortunately we have been allowed the liberty, by that distinguished physician and author, of quoting freely from his works in this brief presentation.

"The first surgeon (chirurgion) to settle in the province of New York," writes Dr. Walsh, "was Harmen Meyndertsen Van den Bogaert, who arrived in New Amsterdam in 1631, as the surgeon of the ship 'Eendracht.' He became surgeon to Fort Orange (now Albany), and was noted for his cordial relations with the Indians, but was a victim to their treachery. O'Callaghan, in his History of New Netherlands, gives the name of an English surgeon, William Beaton (chirurgion to the ship 'William,' of London) who practiced in New Amsterdam. The landing of ship surgeons led the Council of New Amsterdam to request Dr. Johannes La Montagne to issue permits to those sufficiently expert in medicine and surgery to practice in the colony. He also had the additional duty of determining the fitness of the barber surgeons who wanted to practice here. Toner notes the jealousy among the barber surgeons, as well as their frequent lack of skill, and the constant necessity for legal regulation. Dr. La Montagne, a Huguenot from Holland in 1637, was the first regular graduate in medicine to practice in the province, having received his degree from the University of Leyden. He acted as schoolmaster as well as physician, had a seat in the Council, and was vice director in command of Fort Orange. Kiliaen Van Rensselaer in 1642 engaged Abraham Staes to go to the colony as surgeon."

"The first medical book to be published in what is now the United States was Dr. John Jones's "Plan, Concise and Practical Remarks on the Treatment of Wounds and Fractures." The author was the surgeon-general of the Continental troops. Mumford, in his Surgical Memoirs, said

' American surgeons must look back to John Jones of New York as the first of their eminent professional forebears ' Dr Jones was a medical apprentice of Dr Cadwalader, of Philadelphia, the best-known surgeon in the country at that time Thence Jones went to London, to come under the influence of John Hunter and Percival Pott, and to Paris to study under Petit and Le Dran, considered the greatest surgical teachers of the time After a period at Edinburgh under Monro, he returned to America to become surgeon to the American troops in the French and Indian War When he volunteered his services to the colonies during the Revolution, he was appointed surgeon-general and proved just the man for the position The Continentals had the advantage of the best surgery of the time Cadwalader Colden was an eminent physician, who devoted more time to science, government and history than to medicine

" The colonies generally were infested by quacks and medical charlatans, and newspapers were used to advertise their curealls In 1753, a medical regulation act was passed which required that ' all the physicians, surgeons and apothecaries in the province are to be licensed by a board consisting of the four oldest members of his Majesty's Council, the judges of the Supreme Court, the representatives of the City and Assembly, our Mayor and Recorder for the time being, or any seven of them, with the assistance of two physicians and two surgeons by the majority of them elected Until after examination and licensing no one shall practice Examinations shall be public '

" No bills for medical services were collectable unless the practitioner had a license There were already complaints as to exorbitance of doctors' fees, so the bills of physicians were to be submitted to an examiner appointed for that purpose, before presentation to the patient It has been estimated by Toner that at the time of the Revolution there were 3,500 physicians in the colonies, of whom only 400 held the degree of M D A list of thirty-five has been compiled for New York alone

" New York was a pioneer in American medical education According to Dr David Hosack, the founder of the botanical gardens on the site of which Rockefeller Center has been built, the first effort at the formal teaching of medicine in this country was the private course in human anatomy offered in New York City by Dr John Bard and Dr Peter Middleton, probably before 1750 The first formal teaching of anatomy in this country, in connection with an organized educational institution, was a course of lectures given at King's College, now Columbia University, in 1763 by Dr Samuel Clossey, a graduate of Trinity College, Dublin Five years later, Dr Peter Middleton and Dr Samuel Bard, the son of Dr John Bard, the first physician to practice dissection in America, established the medical department of King's College This institution gave the first degree of Bachelor of Medicine in 1769 The first degree of Doctor of Medicine was bestowed in New York in 1770 on Robert Tucker, and the second in

1771 on Samuel Kissam Dr Samuel Bard, professor of the theory and practice of physics in New York, Mumford declares to have been the most eminent physician of his time with the single exception of Dr Rush

"During the Revolution, medical instruction was irregular After the Revolution the Columbia school resumed its classes and suffered severely from the 'Doctors' Riot' which took place in 1788, because of popular opposition to dissection No legal way of obtaining bodies for purposes of dissection existed Resurrectionism, that is the surreptitious removal of the recently buried to the dissecting room, was a common practice On Sunday, April 13, 1788, some boys saw a dissected arm hanging in a window of the medical school, and when they called attention to it, a crowd collected Some of them forcibly entered the building and destroyed many anatomical preparations On Monday morning, a crowd collected around the college, and the mayor attempted to soothe their feelings In the afternoon, the crowd gathered around the jail in which the doctors and medical students had taken refuge because of threatened violence Baron Steuben, of Revolutionary fame, tried to pacify the mob They knocked him down, and so upset his dignity that he quite lost his temper, calling out to the mayor, 'Fire! Duane, fire!' and the militia, summoned for protection, fired, killing seven rioters and wounding many more After this the mob dispersed

"The New York riot led to the passage of a law, in 1789, that 'science might not be injured by preventing the dissection of proper subjects' This law provided that 'when any offender shall be convicted of murder, arson or burglary for which he shall be sentenced to suffer death, the courts may at their discretion add to the judgment that the body of such offender shall be delivered to the surgeons for dissection' This legal provision of the bodies of executed criminals proved utterly inadequate for teaching by dissection, and 'body snatching' continued

"It was more than sixty years after the 'Doctors' Riot,' before a law (1854) was enacted by the New York legislature, granting unclaimed bodies for anatomical purposes Many prominent physicians recalled, later in life, unearthing bodies from cemeteries on Long Island, when they were students, and smuggling them across the ferry Dr Hartwell, in his lecture on 'The Hindrances to Anatomical Study in the United States, Including a Special Record of the Struggles of Our Early Anatomical Teachers,' tells of incidents similar to the Doctors' Riot in other cities

"The Medical School of Columbia College was united in 1814 with the College of Physicians and Surgeons in the City of New York which had been incorporated in 1807 Not for a number of years were these pioneer medical schools followed by others—the New York Medical College (1850), the short-lived Metropolitan Medical College (1857–62), the Homeopathic Medical College (1860), the Bellevue Hospital Medical College (1861), and the Eclectic Medical College (1865)

"The first medical college in the state outside of the metropolis was the College of Physicians and Surgeons of the Western District of the State of New York, established at Fairfield, in 1809. After incorporation in 1812, this College continued to function until 1840, having graduated 609 physicians. Geneva Medical College, established in 1835, and Albany Medical College, incorporated in 1838, continued to advance medical education. The number of medical colleges increased, until in 1882 there were 13, with 2,982 students, and property valued at more than \$703,000. The first woman in the United States to receive the degree of Doctor of Medicine was Elizabeth Blackwell, who graduated from the Geneva Medical College in 1849. Fifteen years later, the New York Medical College for Women was incorporated, to be followed in 1866 by the Women's College of Physicians and Surgeons. At the present time (1936), there are in the state 9 medical colleges with 2,507 students enrolled.

"New York's priority in this country in the provision of postgraduate education for physicians is worth noting. Struggling practitioners of medicine who had received very limited medical education and were sincerely desirous of doing better professional work, could take several months from their practice and spend these at postgraduate study, to the decided advantage of themselves and their patients. The first of these graduate medical schools was the New York Polyclinic, founded in 1882 by Dr. John Allen Wyeth, himself a distinguished surgeon, one of the many progressive workers in surgery whom New York owes to the South. He had served with distinction in the Confederate army, and was looked upon as a leader in the profession. He is honored by a statue to him on the grounds of the capitol of Montgomery, Alabama, his native state. The postgraduate work in medicine that he initiated was taken up in other cities throughout the country and came to be a valued feature of American medical teaching.

"Dr. Valentine Seaman, at New York Hospital, was the pioneer in this country in the training of nurses. The inscription below his portrait in the hospital commemorates this: 'In 1798 he organized in the New York Hospital the first regular training school for nurses, from which other schools have since been established and extended their blessings throughout the country.' In 1872, Bellevue Hospital secured Nightingale nurses and thus introduced the modern trained nurse into America. Up to this time, the nurses at Bellevue were mainly women who had been sentenced to the workhouse, which constituted one part of Bellevue under the commissioner of charities and correction. After sobering up, they were transferred to the hospital as nurses, if they had had any experience in family nursing. When the Nightingale nurses came from London, these women stoned them and called them 'scabs' and 'blacklegs,' imported from England to take the jobs of good Americans.

"Bellevue was about as insanitary as a hospital could possibly be. Its death rate was extremely high. Infection was always rife. Erysipelas

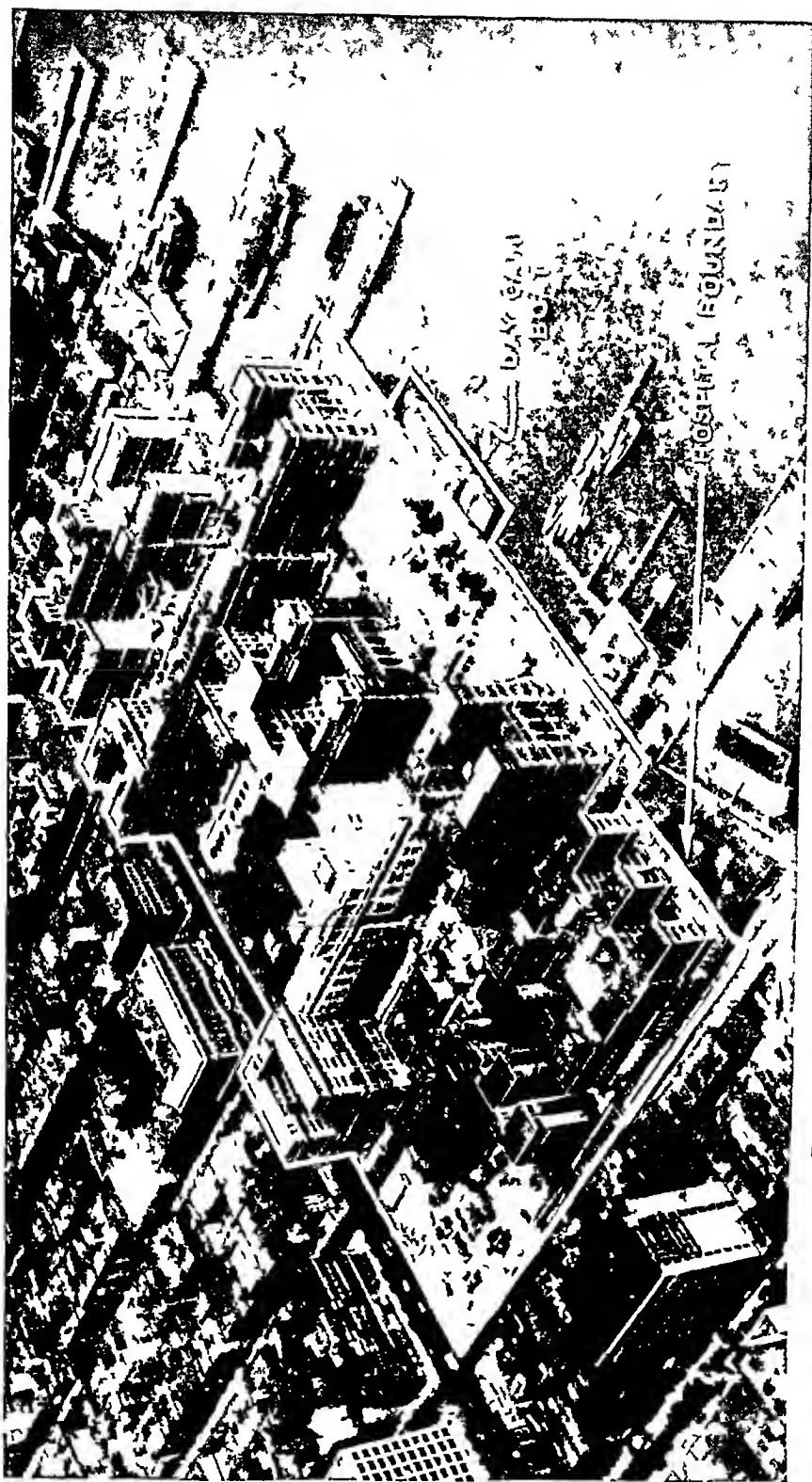


FIG 1 Bellevue Hospital (By permission of the New York Daily News)

often proved fatal to surgical patients. No wonder the poor dreaded the hospital, though this was true of hospitals everywhere. It was almost worse to go to a hospital than to the poorhouse. Pasteur's discoveries in bacteriology, applied by Lister to surgery, reformed hospitals, though not until well toward the end of the nineteenth century. The trained nurse proved a valuable factor in this consummation so urgently needed."

MEDICINE IN NEW YORK TODAY

New York City's opportunities for medical education are extensive. In all, there are 183 hospitals approved by the American Medical Association, with 837 approved internships available annually, and offering 396 annually available approved "residencies." Fifteen institutions offer post-graduate instruction.

Five medical schools are located in New York City: Columbia University College of Physicians and Surgeons, Cornell University Medical College, Long Island College of Medicine, New York Homeopathic College and Hospital, and New York University College of Medicine.

New York City is divided into five counties by boroughs: New York, Kings (Brooklyn), Queens, Bronx and Richmond (Staten Island). In each of these there is a county medical society which is an integral part of the Medical Society of the State of New York and the American Medical Association. Their membership comprises: New York, 4,755, Kings, 2,645, Queens, 809, Bronx, 1,247, and Richmond, 122.

The New York Academy of Medicine, at 2 East 103rd Street, Manhattan, was organized in 1847 and exists to advance medical knowledge. Its library is the second largest in the United States, containing 224,000 volumes. In Brooklyn, the Medical Society of the County of Kings has affiliated with it an Academy of Medicine at 1313 Bedford Avenue, Brooklyn, with a medical library ranking fourth in size in the country, containing 143,000 volumes. Both libraries contain many thousands of pamphlets and current medical journals available for reference.

During the course of the annual session, clinics and demonstrations will be held in the following hospitals: Bellevue, New York Hospital, Long Island College Hospital, St. Luke's, Roosevelt, Mt. Sinai, Presbyterian, and Post-Graduate Medical School and Hospital, also at the Rockefeller Institute for Medical Research and the Department of Health of New York City.

Bellevue Hospital—Bellevue Hospital is located at the foot of East 26th Street. It is the oldest hospital in the United States. Established in 1736, it was then known as the "Almshouse." In 1844 the teaching of medical students was begun and now the facilities of the hospital are utilized for teaching purposes by New York University, The College of Physicians and

Surgeons, Columbia University and by Cornell University Medical College. The Medical and Surgical Divisions are under the supervision of the Commissioner of Hospitals. The Training School for Nurses was opened in 1873. In 1887 a Training School for Male Nurses was begun. The present bed capacity is 2,431 and during 1938 the new Chest Building will be opened, adding an additional 360 beds. The hospital maintains a large Out-Patient Department and 612,378 patients' visits were cared for during the year 1937. The staff consists of a medical superintendent and assistant superintendents, 550 visiting physicians, 28 resident physicians, 198 interns and more than 1,000 nurses.



FIG 2 New York Hospital—Cornell Medical Center

New York Hospital (York Avenue and 68th Street) The Society of the New York Hospital was chartered in 1771 during the reign of George III, and during the Revolutionary War the hospital was used by the British. Since that time it has been a teaching hospital, and from 1912 its principal teaching affiliation has been with Cornell University Medical College. In 1932 the following institutions moved into the same group of buildings:

Society of the New York Hospital, Society of the Lying-In Hospital of the City of New York, Manhattan Maternity and Dispensary, New York Nursery and Child's Hospital, and Cornell University Medical College. The "New York Hospital—Cornell Medical College Association" is an informal committee which serves as a medium for coordinating the joint activities of the two institutions. Ground was broken for the Medical Center in 1929. The cost of the Center was approximately \$15,000,000. The main building is twenty-six stories high.

Long Island College Hospital (Henry and Pacific Streets, Brooklyn). Founded in 1858, this was the first medical college in the United States to incorporate its own hospital.

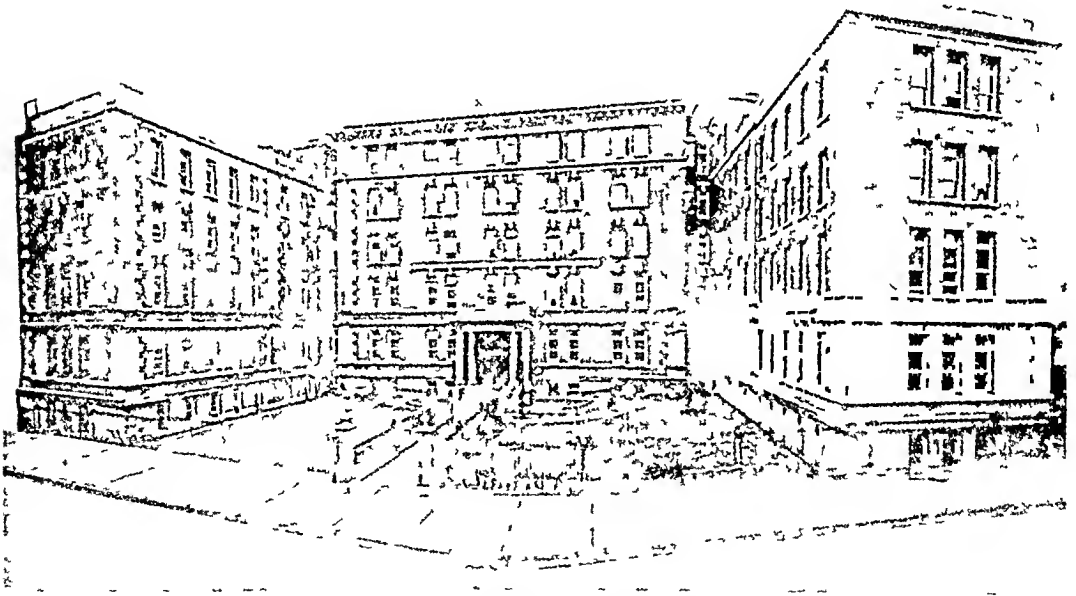


FIG 3 Long Island College Hospital

The first course of lectures at the Medical School began on March 30, 1860. In this same year the number of hospital beds was increased to provide for the many sick and wounded soldiers of the Civil War. The Long Island College Hospital was the first hospital in the Metropolitan District to receive wounded soldiers for nursing and medical treatment. The Long Island College Hospital has grown from an infant institution of twenty-five beds, housed in a private dwelling, to a modern hospital of 486 beds, a modern laboratory, a nurses home and a clinic treating 123,819

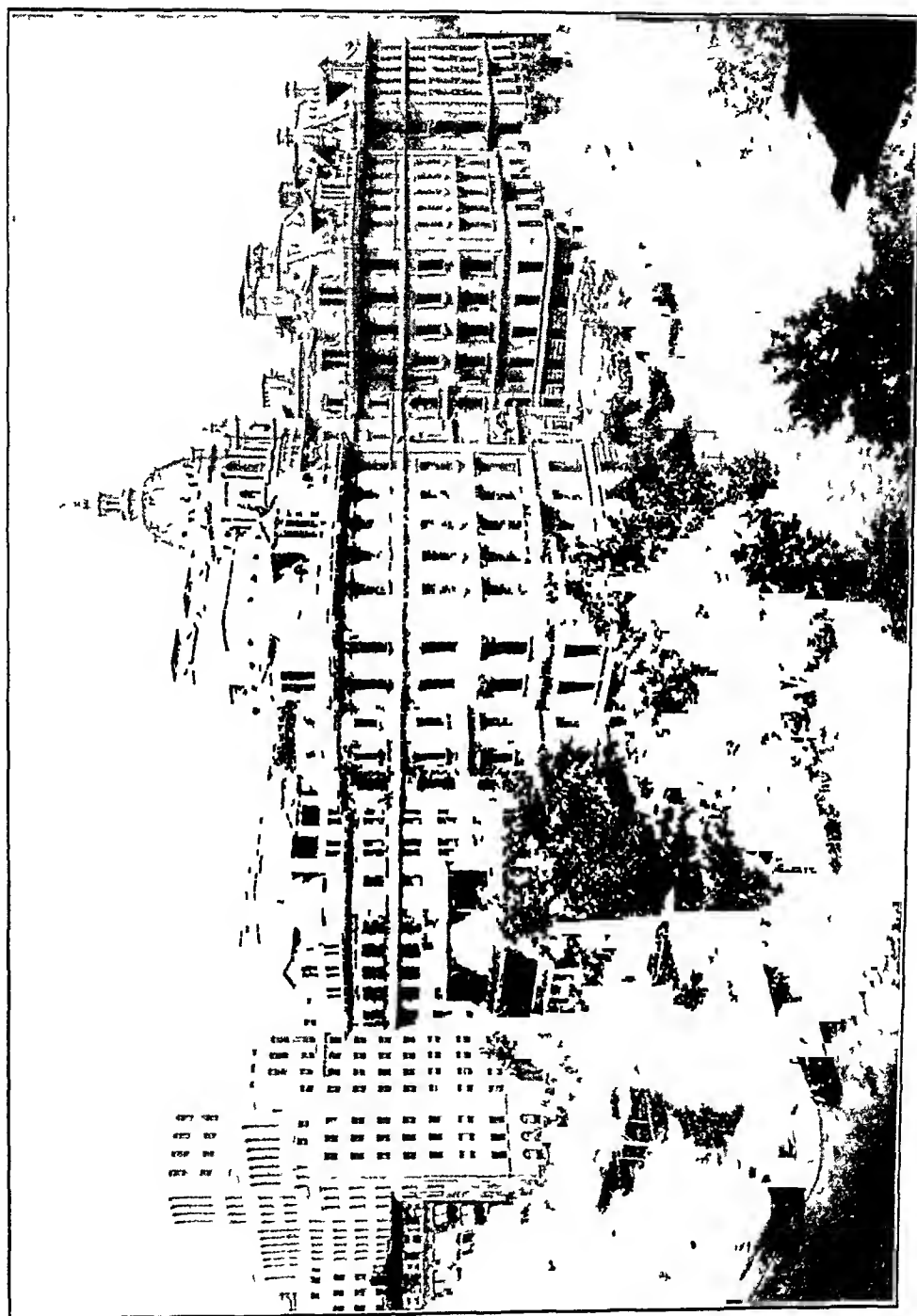


FIG 4 St Luke's Hospital

patients a year. In 1930 the college and the hospital separated, the college changing its name to the Long Island College of Medicine. It still uses the hospital freely in teaching. The present hospital building is about thirty years old, while the Polhemus Memorial Clinic was built in 1896. The Hoagland Laboratory (1887), which was the first bacteriological laboratory built in the United States, and the Polak Laboratory (1931), are included in the group of buildings about the college.

St Luke's Hospital (Cathedral Heights, 113th Street and Amsterdam Avenue) The hospital is open at all times for medical and surgical aid and nursing to the sick, and disabled from acute, curable, non-contagious

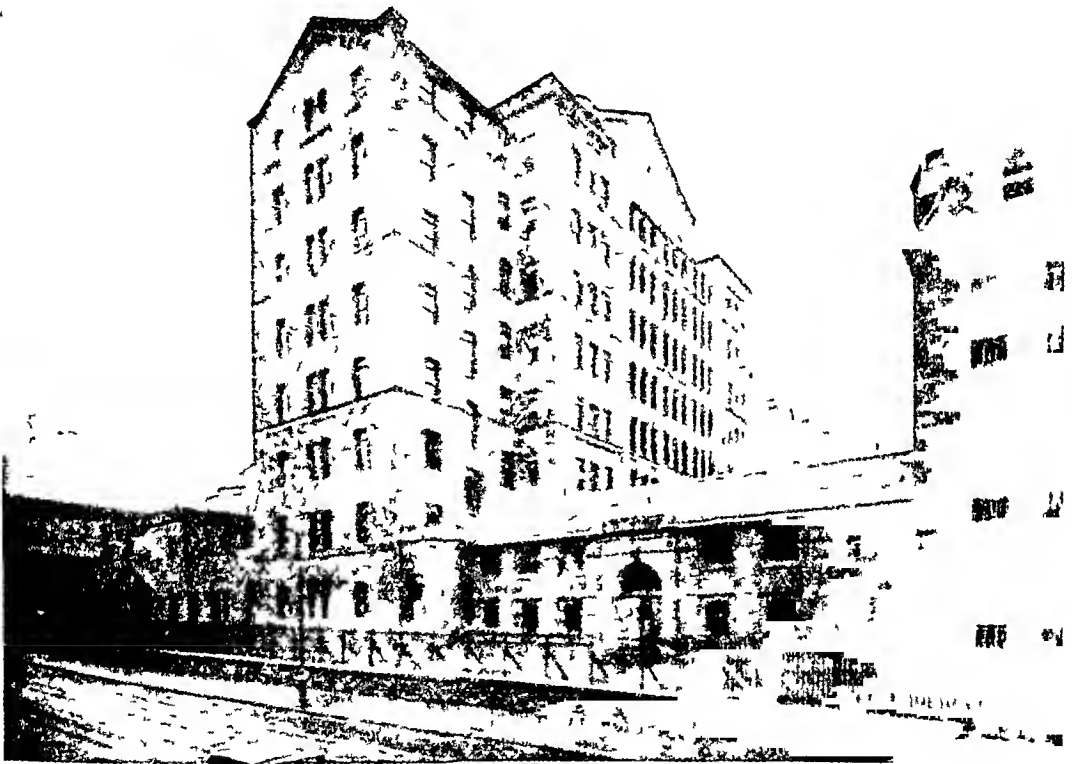


FIG 5 Roosevelt Hospital

diseases, without distinction of race or color. Cases demanding immediate care are received at any hour of the day or night. The hospital is supported by voluntary contributions and endowments. It is free to those unable to pay for services. St. Luke's also maintains a dispensary, training school for nurses and a hospital service.

Roosevelt Hospital (Ninth Avenue and 59th Street) Roosevelt Hospital was opened in 1871. It is a general hospital with 391 beds. In 1936



FIG 6 Mt Sinai Hospital

there were 7 351 patients admitted and 66 085 visits were made to the Out-Patient Department. It is used for clinical teaching by the College of Physicians and Surgeons of Columbia University. A training school for nurses and an emergency department are conducted by the institution.

Mt Sinai Hospital (Fifth and Madison Avenues between 100th and 101st Streets). Organized in 1852 for "benevolent, charitable and scientific purposes." The work of the hospital was begun in a small private dwelling on 28th Street between 7th and 8th Avenues. It accommodated 28 patients. The hospital now has accommodations for 856 patients, including eighteen beds in the Receiving Ward, 250,000 visits are made annually to its Out-Patient Clinic. Mt Sinai created a precedent among the hospitals in New York in 1878 by setting up a distinct pediatric service, and

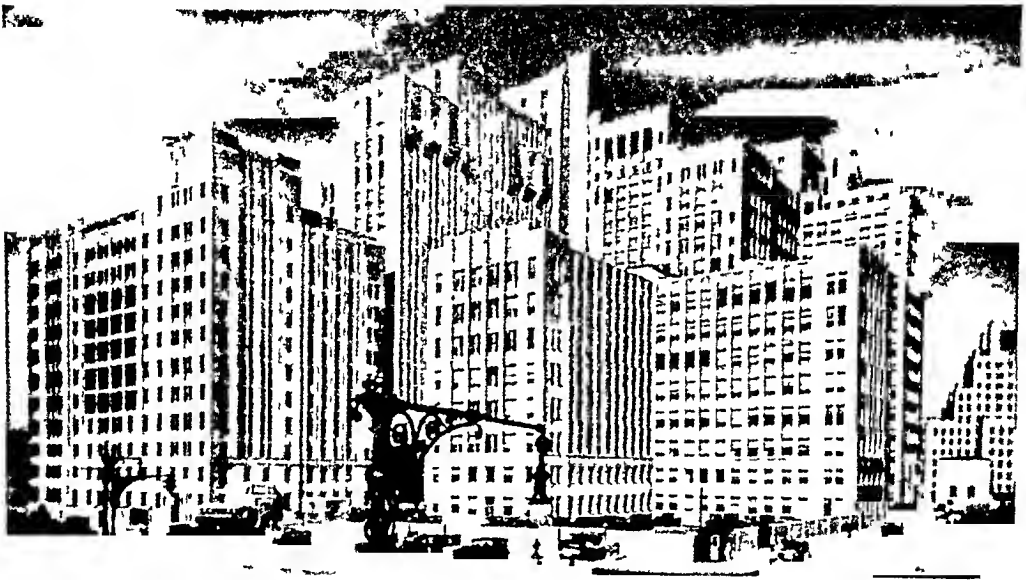


FIG 7 Columbia-Presbyterian Medical Center

an otological service in 1879. There is a training school for nurses in connection with Mt Sinai, which was incorporated in 1881. The present hospital was completed and occupied March 15, 1904. Additions to the original group of buildings have been made continuously since that time. The Research Foundation of the Mt Sinai Hospital was incorporated in 1936, "to conduct, promote, encourage and assist investigation in the services and arts of hygiene, medicine, surgery and allied subjects."

Presbyterian Hospital. Located with twelve other units composing the "Medical Center" at Broadway and 168th Street, it was founded in 1876, and is affiliated with the College of Physicians and Surgeons the Medical

Department of Columbia University The Hospital moved into the present buildings in 1928 On the present site are grouped, besides the Presbyterian Hospital and the College of Physicians and Surgeons of Columbia University, the Sloan Hospital for Women, the New York State Psychiatric Institute and Hospital, the Babies' Hospital, the Squier Urological Clinic, Presbyterian Hospital and Sloane Hospital Schools of Nursing, the Neurological Institute and Hospital, the Stephen V Harkness Patient Pavilion, the School of Dental and Oral Surgery, the Vanderbilt Clinic, the Eye Institute, and the DeLamar Institute of Public Health There are 1,674 beds

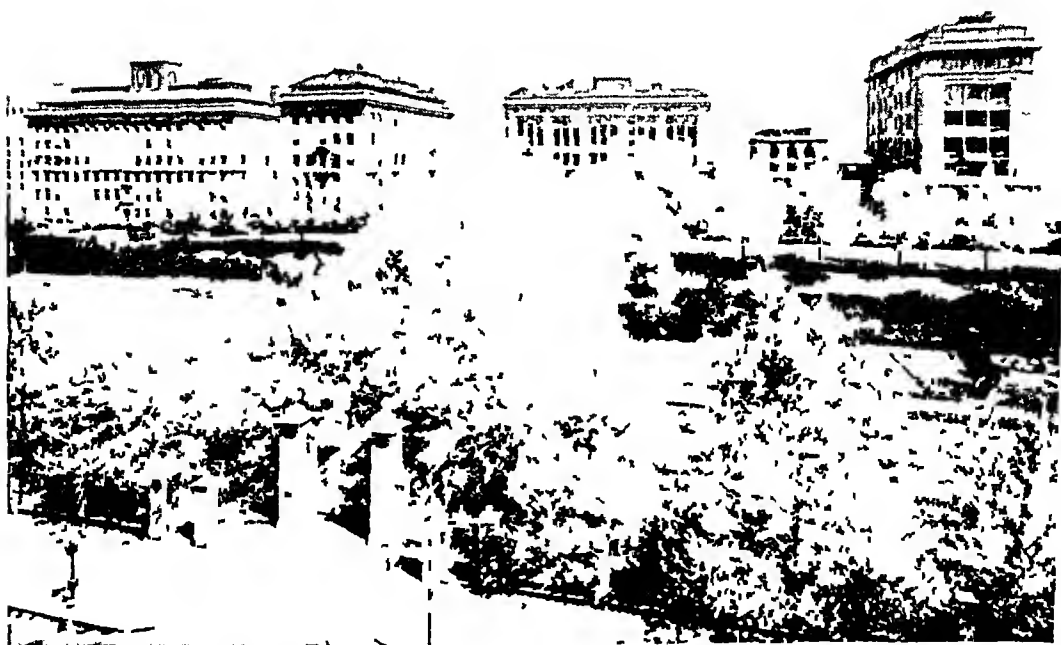


FIG 8 Buildings of the Rockefeller Institute for Medical Research, New York The Laboratory Buildings are shown to the left The Hospital Building and Isolation Building are at the right in the photograph

The entire Medical Center, known as the Columbia-Presbyterian Medical Center, of which the Presbyterian Hospital is a part, covers twenty-two acres and cost \$25,000,000

Rockefeller Institute for Medical Research (York Avenue and 68th Street) The Hospital of The Rockefeller Institute for Medical Research was opened in 1910 The principles of organization of the Hospital were first, that the number of diseases studied at any one time would be limited

and only patients suffering from one or another of the diseases under investigation would be accepted, second, that all the scientific staff was to devote its entire time to the duties of the Hospital, third, that the work of the Hospital staff should consist not merely in observational studies, but in experimental studies equally, and fourth, that no charge was to be exacted from the patients for services rendered. These principles have been strictly followed. The Hospital has 60 beds and an Out-Patient Department.

New York Post-Graduate Medical School and Hospital Location 30 East 20th Street. The oldest institution in this country engaged solely in the teaching of graduate medicine, having been founded in 1882. The School was incorporated into the educational system of Columbia University

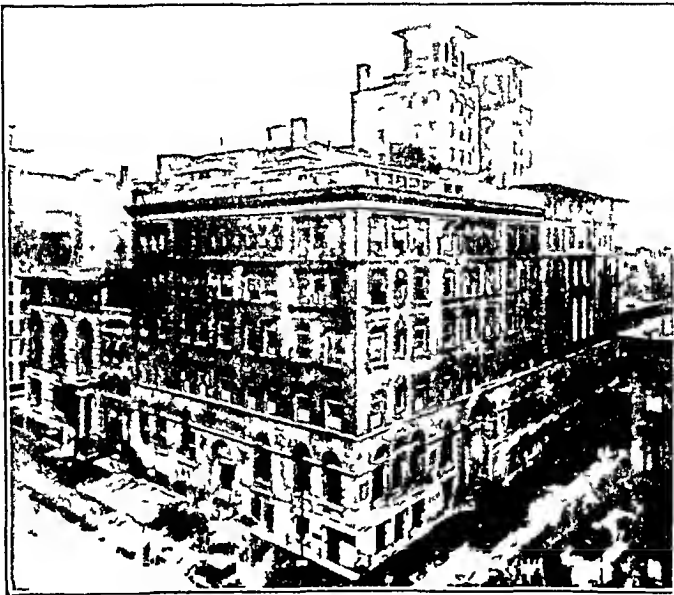


FIG 9 New York Post-Graduate Medical School and Hospital

in January 1931 and registers more than five hundred physicians annually. The Hospital maintains 410 beds and an out-patient service notable for the variety and size of its clinics. There are two extramural units: the Reconstruction Hospital with 65 beds for accident cases and conditions arising out of industrial injury and disease, and the former New York Skin and Cancer Hospital now operated as an out-patient service for skin and cancer cases only, the in-patients being hospitalized in the main hospital building. Certain wards of the Metropolitan, Willard Parker and Sea View Hospitals, and the Hospital for Joint Diseases are also used for teaching purposes.

The *New York City Department of Health* operates seventeen clinics for the diagnosis of syphilis, gonorrhea, and lymphogranuloma inguinale. Ten of these clinics are also treatment centers. Annually, about 24,000 patients make over 400,000 visits to these clinics which conduct 120 sessions per week, serving all parts of the city. For the clinical demonstration arranged for the American College of Physicians, cases will be selected from these clinics and brought to the new Health Department Building at 125 Worth Street.

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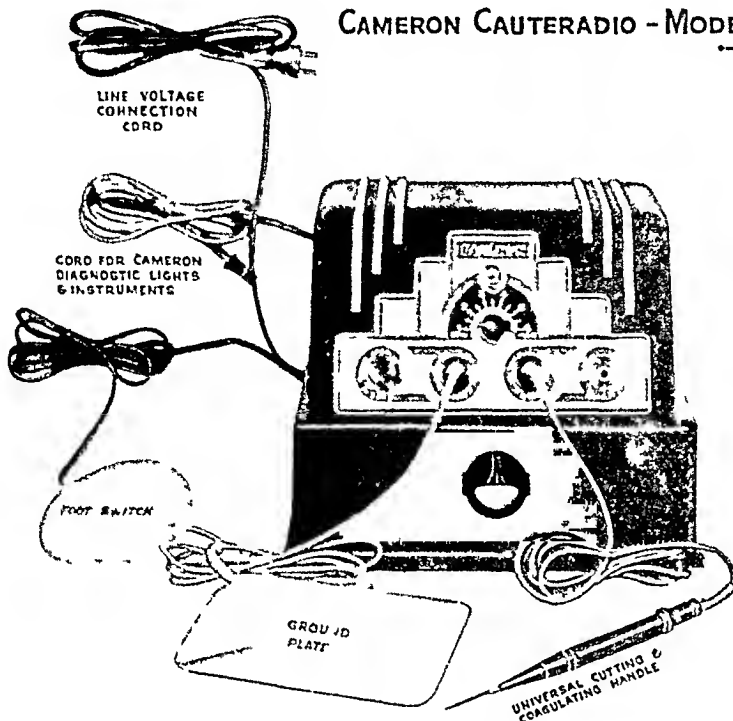
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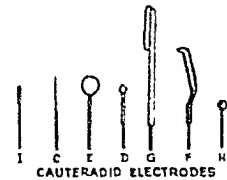
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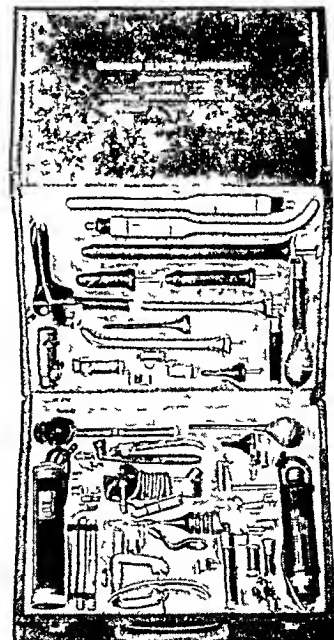


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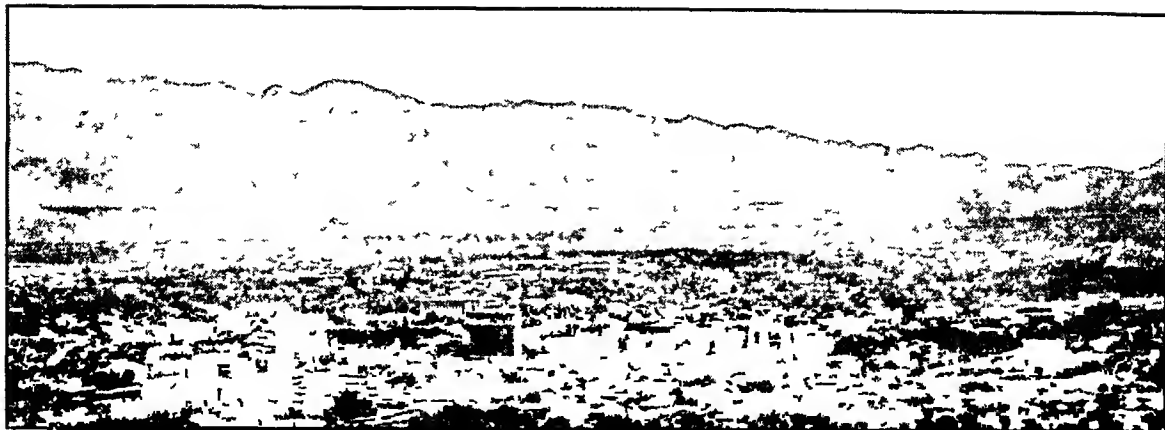
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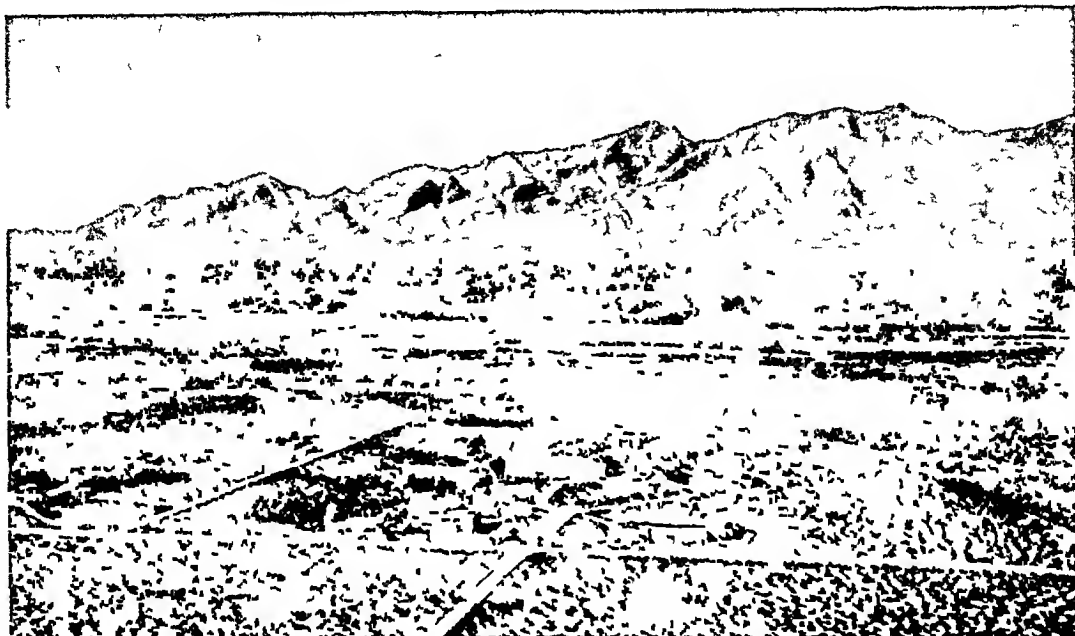


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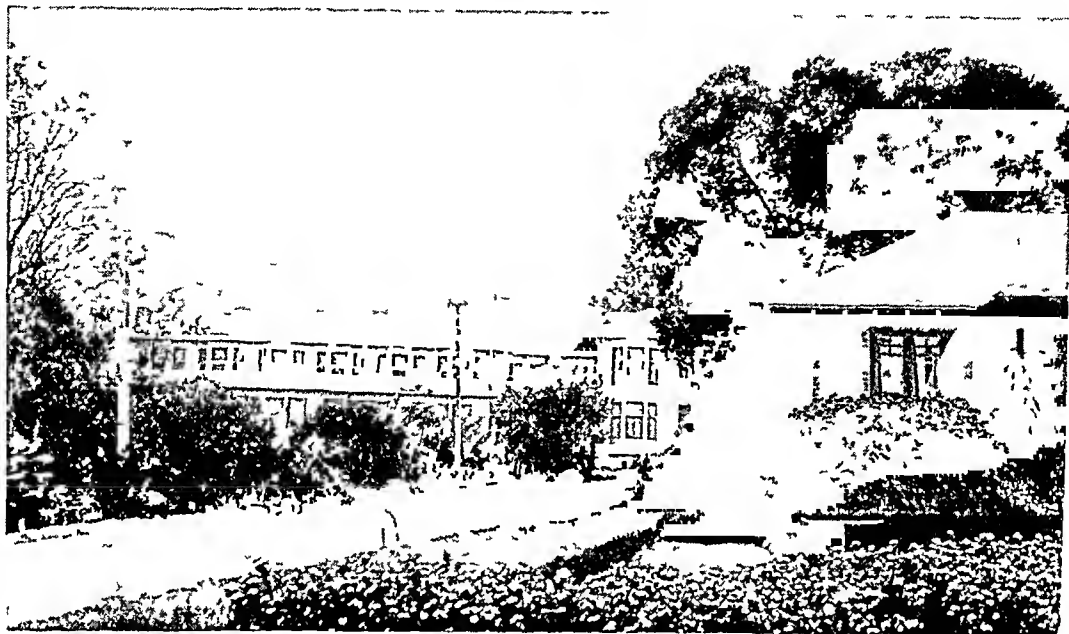
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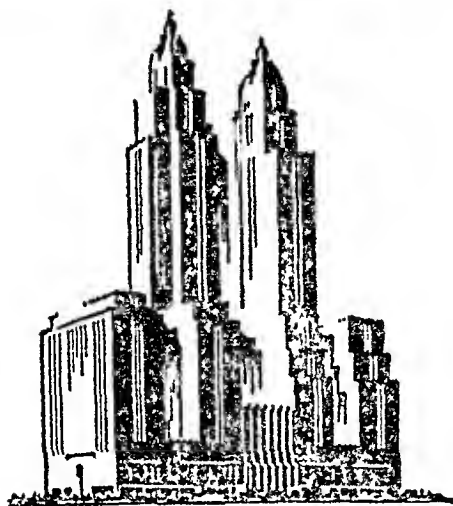
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OFFICIAL PERIODICAL OF THE AMERICAN COLLEGE OF PHYSICIANS

Place of Publication—Prince and Lemon Sts, Lancaster, Pa

Editorial Office—University Hospital,
Baltimore, Md

Executive Office—4200 Pine Street,
Philadelphia, Pa

THE ANNALS OF INTERNAL MEDICINE is published by the American College of Physicians. The contents consist of contributions in the field of internal medicine, editorials, book reviews, and a section devoted to the affairs of the College.

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extract orally were able to modify human diabetes. Further evidence that the hypoglycemic action is not due to an insulin extract from the duodenum has been supplied by Zunz and La Barre⁵⁶. Using the method of pancreatico-jugular anastomosis between adrenal decapsulated dogs, they obtained a lowering of blood sugar after intravenous injection of non-hypotensive secretin in the donor that was much less marked than that in the recipient. This, of course, would not be expected to occur, if the extract were insulin.

Other differences in the action of the duodenal extracts as compared with insulin may be noted in the work of still other investigators. Thus, Takacs⁵² reports that in many instances his duodenal extract produced a very conspicuous reduction of blood sugar (50 to 60 per cent) without the phenomena that go with insulin hypoglycemia. Such hypoglycemic phenomena did not appear even after the administration of very large doses of the extract. Duncan^{18, 19, 22} too, recently remarked the fact that while they found their extract of value in reducing a marked hyperglycemia in human diabetics, they never saw any hypoglycemic reactions from the use of the extract. And Novao Santos⁴⁷ reports a case of a controlled diabetic in whom the injection of secretin produced, after two hours, a blood sugar of 38 mg per 100 c.c., with no symptoms of a hypoglycemia. Takacs⁵² also points out the much greater duration of the effect of his extract as compared with that of insulin. Secretin, from this standpoint the observations of La Barre and Ledrut²⁷ and of Haston²⁸ are also of interest. These investigators found that not only were they able to keep depancreatized dogs alive by the oral administration of the duodenal preparation, but also that they did not find it necessary to compensate for the absence of pancreatic ferments—a procedure which was indispensable in the treatment of a depancreatized animal with insulin.

He noted
at the d

III IS THE HYPOGLYCEMIC EFFECT OF DUODENAL EXTRACTS DUE TO ISLET STIMULATION?

In 1924, Troteano,⁵³ on the basis of experiments on dogs, concluded that the transitory hypoglycemic effect which follows the intravenous injection of secretin results from the stimulation of the insular apparatus of the pancreas. Many investigators since have supported this view. Dale⁹ as far back as 1905 observed in both mammals and amphibia an increase in the number and volume of the islets of Langerhans after repeated injections of secretin. This work of Dale's was referred to in the report of Laughton and Macallum,³² made a quarter-century later. These investigators found that animals receiving their duodenal preparation daily, over a period ranging from a week to 10 days, showed the effect on artificially induced hyperglycemia for two weeks following the last injection. This result they explain in terms of the islet-stimulation concept. Macallum³⁵ had previously postulated that diabetes might result from insular fatigue.

occasioned by the excessive stimulation of the islets by the duodenal hormone. Freud and Saadi-Nazim¹⁵ in 1926 further confirmed Troteano⁵³ by their results from the duodenal instillation of hydrochloric acid in dogs. In the same year, Dixon and Wadia¹⁰ demonstrated the increase in pituitrin in the cerebrospinal fluid of dogs following the injection of duodenal extracts, a reaction which they believed to be of the same nature as that which followed injections of insulin. The following year Fieschi,¹⁴ using secretin manufactured by the original Bayliss and Starling formula, noted that the sugar tolerance in dogs whose diet was rigorously controlled increased after prolonged treatment with secretin. Fieschi injected 10 cc three times a day for nearly 30 days. He noted that some of the animals which had a low tolerance at the beginning of treatment almost doubled their tolerance to ingested sugar by the end of the treatment. Uselli⁵⁴ believed that the hyperemia of the pancreas which followed the injection of secretin, or the introduction of hydrochloric acid into the duodenum, determined the hyperactivity of both the external and insular secretory mechanism.

Gley and Hazard¹⁶ from transfusion experiments following the duodenal instillation of hydrochloric acid concluded that the mechanism involved was islet stimulation. Finally, La Barre and Houssa²⁶ studied the effect of secretin produced in the duodenum upon a pancreas the exocrine portion of which had been destroyed. Injected into the duodenum of a dog whose external pancreatic ducts had been ligated one to two months previously, and in which a bilateral suprarenal glandectomy had been performed just before the injection, these investigators observed a gradual hypoglycemia as marked in these animals as in those with atrophic pancreas. They obtained a similar response even when the external portion of the pancreas adhering to the duodenum was removed and the remaining portion maintained as an abdominal subcutaneous graft.

The above cited investigations appear to indicate that the blood sugar reducing factor present in duodenal extracts operates through islet stimulation. To prove absolutely that this is the sole mode of action of the duodenal extract it would be necessary to show that it could not alter blood sugar without the aid of the pancreatic islet tissue. The obvious approach was the study of its action in the totally depancreatized animal.

IV. IS THE HYPOLYCEMIC ACTION OF DUODENAL EXTRACTS DUE TO A SEPARATE DUODENAL HORMONE?

Oehme and Wimmers³⁹ in 1923 reported a hypoglycemic effect from secretin in four depancreatized dogs. The following year Ivy and Fischer²² obtained an insulin-like substance from the duodenal mucosa with which they were able to reduce the blood sugar in a depancreatized dog. Penau and Simonnet^{41, 42} reported similarly. Takacs⁵² found his duodenal preparation effective in depancreatized animals when administered intravenously, subcutaneously, orally or by rectum. La Barre and Still²⁴ also reported

the efficacy of crude secretin in lowering the blood sugar of totally diabetic dogs, and La Barre and Ledrut²⁷ were able to obtain through the hydrolysis of secretin, a non-secretagogic fraction which was especially effective in reducing the blood sugar of depancreatized animals. Other observers such as Novao Santos,^{15, 46} Criado,⁸ Laughton, Macallum, Rabinowitch and Watson,³¹ and Laughton and Macallum³² were unable to influence the blood sugar of depancreatized animals with their duodenal extracts. In such investigations, however, positive findings, if repeated, are more significant than negative results.

V IS THE HYPOGLYCEMIC ACTION OF DUODENAL EXTRACTS A COMBINATION OF ISLET STIMULATION AND DIRECT ACTION?

While the results obtained by certain investigators in the depancreatized animals indicate that the duodenal extracts are capable, alone, of reducing the blood sugar, there is some evidence that in the intact animal they enhance islet activity as well. Zunz and La Barre⁵⁷ have shown that secretin can increase the output of insulin. Using adrenalectomized dogs with pancreatico-jugular anastomoses, they found that purified secretin injected into the donor dog caused a drop in blood sugar in both the donor and recipient, with the fall more marked in the latter. Since in this experiment, the donor is physiologically depancreatized, the above results may be interpreted as a double action of the secretin. This concept is fortified by their findings with jugulo-jugular anastomosis: the injection of secretin into the donor produced only a slight decline in the recipient which was less marked than that which occurred in the donor. La Barre and Still reported confirmation of some of these experiments.

Additional suggestive data for the dual action are to be found in the results of Takacs⁵². He noted that depression of the blood sugar following the administration of the duodenal preparation lasted a much shorter time in the depancreatized animal than in the intact one. Clinically, too, both Laughton et al³¹ and Duncan and his associates¹² report their best results with the Laughton-Macallum extract in the milder cases of diabetes.

Our experiments in human beings offer data which do not seem to confirm exactly the probable mechanism as observed in lower animals. It is, of course, impossible to duplicate in man the experimental conditions of animals which permit a study of the effect on the blood sugar of duodenal stimulation in the absence of the pancreas. The closest simulation to such conditions probably was obtained in our case in chart 7. Unfortunately, this man who appeared to have a diffuse calcification of the pancreas was available for only a few studies. It would appear from comparison of chart 7 with the remaining charts that, in man, by far the major effect on the blood sugar of duodenal stimulation is due to islet stimulation rather than to the direct action of a duodenal hormone. This is supported by the greater efficacy of duodenal extracts in the milder cases of clinical diabetes.

THE RELATIONSHIP OF THE HYPOLYCEMIC DUODENAL FACTOR TO THE AUTONOMIC NERVOUS SYSTEM

Despite the studies of Zunz and La Barie¹⁷ which showed that vagotomy does not prevent the action of the sugar reducing factor in injected duodenal extracts, it would appear from the work of Heller²⁰ that some of this action

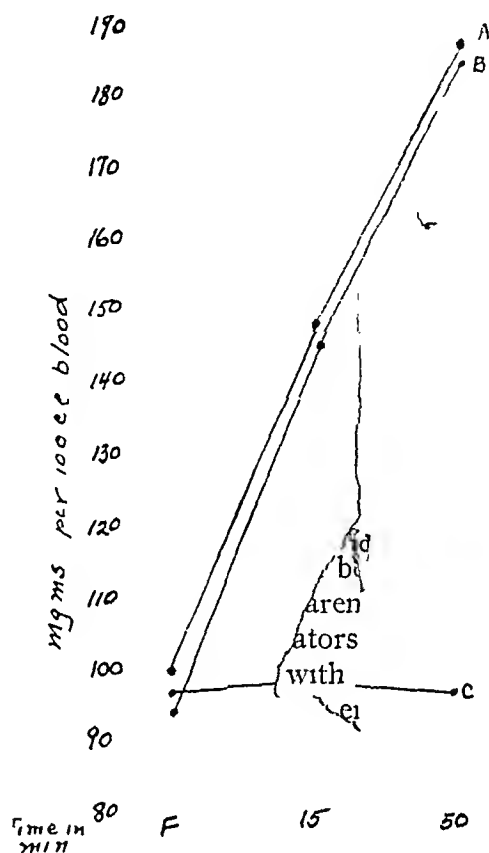


CHART 1

Curve A = Blood sugar readings (F) fasting and at 15 and 30 min after the ingestion of 225 c.c. of 38.4% glucose. No duodenal instillation. Total glucose lost from stomach in 30 min = 25.5 gm.

Curve B = Blood sugar readings (F) fasting and at 15 and 30 min after the duodenal instillation of 20 gm of glucose in isotonic solution.

Curve C = Blood sugar readings (F) fasting and at 15 and 30 min after the ingestion of 225 c.c. of 41.5% glucose and simultaneous duodenal instillation of 0.47% HCl at 100 gtt/s per min. Total glucose lost from stomach in 30 min = 20.6 gm.

was dependent upon intact vagi. This investigator found, by chemical elimination of the vagus by atropine and of the sympathetics by ergotamine, that while the action of the intestinal extract was retained, its effect was reduced.

Whether the duodenal extracts are able to influence adrenalin hyperglycemia is not quite clear. Laughton and Macallum²² report a marked lowering of the level of adrenalin hyperglycemia in rabbits and dogs by

injection of the duodenal extract Hellei²⁰ saw an effect from his extracts under similar conditions, but not a very distinct one

We are not familiar with any previous studies on man of the influence of direct duodenal stimulation on hyperglycemia so produced We studied this effect in 10 patients After intubation of the duodenum of a fasting subject we injected 10 minims of adrenalin chloride (1-1000) subcutan-

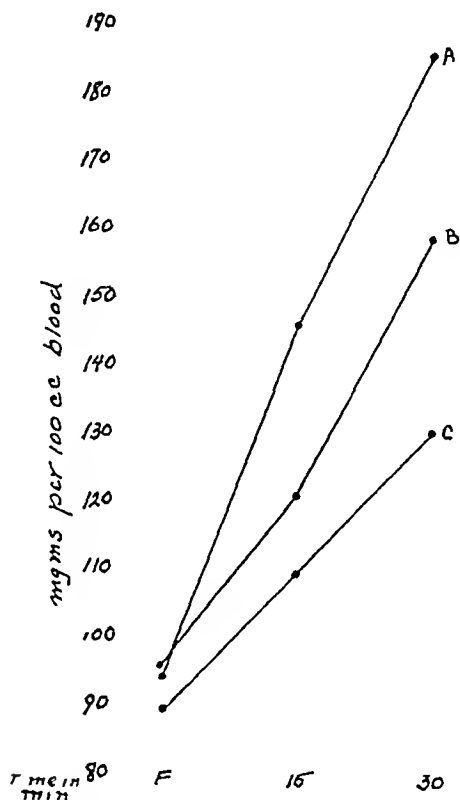


CHART 2

Curve A = Blood sugar readings (F) fasting and at 15 and 30 min after the duodenal instillation of 25 gm of glucose in isotonic solution

Curve B = Blood sugar readings (F) fasting and at 15 and 30 min after the duodenal instillation of 62.5 cc of 40% glucose (25 gm)

Curve C = Blood sugar readings (F) fasting and at 15 and 30 min after the duodenal instillation of 500 cc of 5% glucose (25 gm) in 0.3% HCl

eously, having previously taken blood for sugar determination Blood samples were taken at 15 minute intervals for one hour during which nothing was instilled into the duodenum On a subsequent day the same procedure was repeated, except that, in addition, the duodenal instillation of 0.4 per cent hydrochloric acid at the rate of 60 to 80 drops per minute was started simultaneously with the injection of the adrenalin, and was continued throughout the hour of the test period On still another day the duodenal instillation of the acid was started 15 minutes before the injection of the adrenalin Charts 8 and 9 illustrate the results obtained, the former in a patient with a normal gastric secretion, the latter in a case of anacidity

In chart 8, we note that the subcutaneous injection of 10 minims of adrenalin chloride (1-1000) after an overnight fast produced a change in glycemia from 98 mg to 178 mg per 100 c c in the course of an hour, a rise of 85 mg. Under similar conditions of adrenalin action, the simultaneous instillation of 0.5 per cent hydrochloric acid at the rate of 60 drops per minute during the course of the hour, resulted in a change in blood sugar concentration from a fasting level of 87 mg to 186 mg per 100 c c, a rise

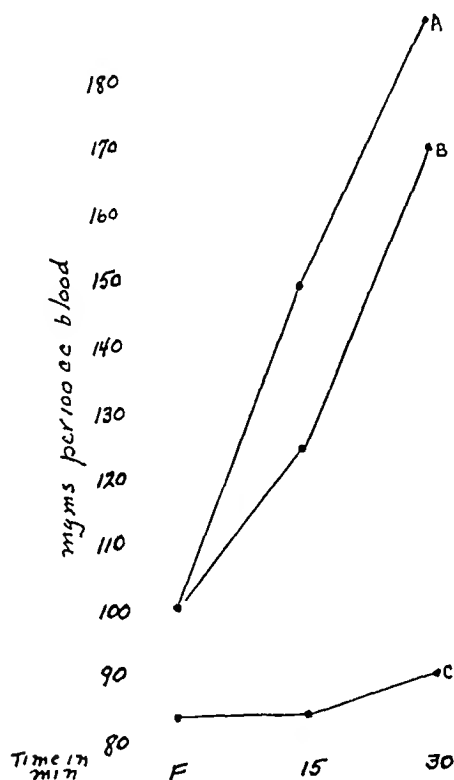


CHART 3

Curve *A* = Blood sugar readings (*F*) fasting and 15 and 30 min after the ingestion of 225 c c of 38.4% glucose. No duodenal instillation. Total glucose lost from stomach in 30 min = 25.5 gm.

Curve *B* = Duodenal instillation of 0.47% HCl at 100 drops per min for 15 min. Acid stopped. Then duodenal instillation of 500 c c of 5% glucose (rapidly). Blood sugar (*F*) fasting at 15 and 30 min after the instillation of the glucose (25 gm).

Curve *C* = Duodenal instillation of 0.47% HCl at 100 drops per min for 15 min. Acid stopped. Then duodenal instillation of 50 c c of 50% glucose. Blood sugar (*F*) fasting and at 15 and 30 min after the instillation of the glucose (25 gm).

of 99 mg per 100 c c of blood. Starting the duodenal instillation of the acid 15 minutes before the injection of the adrenalin did not alter the result. The changes in chart 9 parallel those recorded in chart 8. Similar results were obtained in all of the 10 cases studied. It is, therefore, evident that duodenal stimulation in man is not capable of modifying adrenalin hyperglycemia.

THE EFFECT OF DUODENAL STIMULANTS OTHER THAN HYDROCHLORIC ACID IN THE PREVENTION OF ALIMENTARY HYPERGLYCEMIA

Bayliss and Starling¹ at first believed that the action of the hydrochloric acid was essential to the extraction of active secretin from the mucosa. It was soon learned, however, that many agents, such as soap, chloral hydrate, sodium chloride, sugar, alcohol, acetone and others, could extract an active secretin under similar conditions.

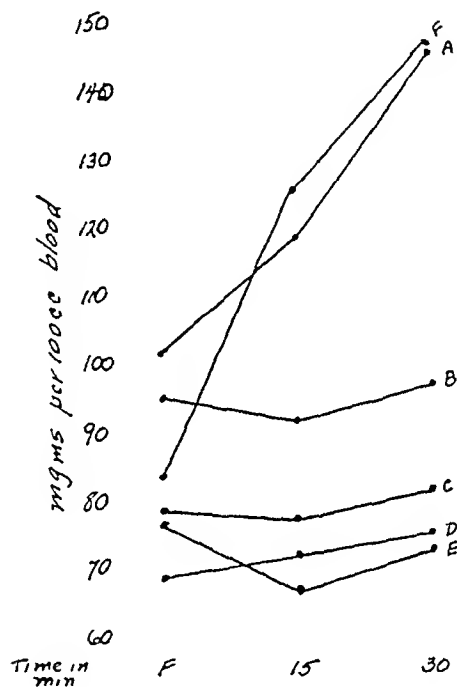


CHART 4

Curve A = Blood sugar readings fasting (F) and at 15 and 30 min after the ingestion of 225 cc of 40.8% glucose. No duodenal instillation. Total glucose lost from stomach in 30 min = 26.4 gm.

Curves B, C, D and E = Blood sugar readings fasting (F) and 15 and 30 min after the ingestion of 225 cc of 40% glucose and simultaneous duodenal instillation of 0.45% HCl at 60, 70, 80 and 100 drops per min respectively. Total glucose lost from stomach in 30 min = 19.9, 18.2, 20.9 and 23 gm respectively.

Curve F = Blood sugar readings fasting (F) and at 15 and 30 min after the duodenal instillation of 23 gm of glucose in isotonic solution.

We⁴⁸ have shown, too, that the intrinsic agent which activates the local duodenal mechanism concerned in the motor activity of the stomach and pylorus, is the gastric hydrochloric acid. It was also pointed out that other substances added in food, which were through chemical or physical action capable of stimulating the duodenal mucosa, could also effect pyloric closure. The present studies were, therefore, extended along these lines and the action of fats, isotonic and hypertonic solutions of sodium bicarbonate and sodium chloride, as well as hypertonic solutions of glucose were investigated. Chart 5 illustrates the effects produced by these various

substances instilled into the duodenum while glucose is being absorbed from the stomach. With oil, hypertonic bicarbonate or hypertonic saline solutions, effects are seen which are identical with those obtained from the duodenal instillation of hydrochloric acid. They consist, as before, of no appreciable rise in blood sugar during the period of duodenal instillation even though quantities of glucose are being absorbed from the stomach which would ordinarily cause a sharp rise in blood sugar. (Curve 4, chart 5.) Chart 6 illustrates a similar action of fat in our diabetic patient.

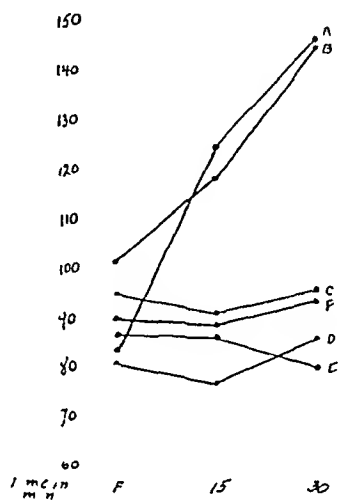


CHART 5

Curve A = Blood sugar readings fasting (*F*) and at 15 and 30 min after the duodenal instillation of 23 gm of glucose in isotonic solution.

Curve B = Blood sugar readings fasting (*F*) and at 15 and 30 min after the ingestion of 225 cc of 40.8% glucose. No duodenal instillation. Total glucose lost from stomach in 30 min = 26.4 gm.

Curve C = Blood sugar readings fasting (*F*) and at 15 and 30 min after the ingestion of 225 cc of 40% glucose and simultaneous duodenal instillation of 0.45% HCl at 60 gtts per min. Total glucose lost from stomach in 30 min = 19.9 gm.

Curve D = Blood sugar readings fasting (*F*) and at 15 and 30 min after the ingestion of 225 cc of 41.0% glucose and simultaneous duodenal instillation of 5% NaCl at 80 gtts per min. Total glucose lost from stomach in 30 min = 21 gm.

Curve E = Blood sugar readings fasting (*F*) and at 15 and 30 min after the ingestion of 225 cc of 40.5% glucose and simultaneous duodenal instillation of olive oil 80 gtts per min. Total glucose lost from stomach in 30 min = 20.2 gm.

Curve F = Blood sugar readings fasting (*F*) and at 15 and 30 min after the ingestion of 225 cc of 39.8% glucose and simultaneous duodenal instillation of sod bicarb (7%) 60 gtts per min. Total glucose lost from stomach in 30 min = 24.2 gm.

Charts 2 and 3 indicate that glucose itself in hypertonic solution in the duodenum calls forth the same mechanism as do other agents. Thus in chart 2, one sees after the duodenal instillation of 25 grams of glucose in isotonic solution a rise in blood sugar from a fasting level of 93 mg to 185 mg in a half hour, a rise of 92 mg of glucose per 100 cc of blood (curve A). When the same amount of glucose in hypertonic solution (40 per cent) is instilled into the duodenum on another day the change in blood sugar concentration in the following half hour is distinctly less marked.

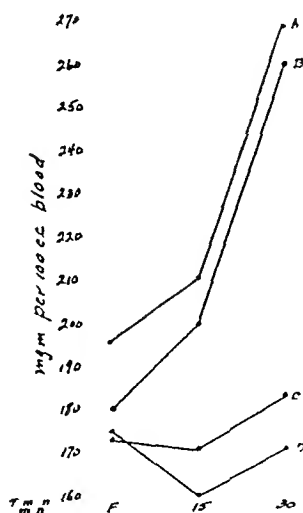


CHART 6

Curve A = Blood sugar readings fasting (F) and at 15 and 30 min after the ingestion of 225 cc of 38.5% glucose. No duodenal instillation. Total glucose lost from stomach 38.6 gm in 30 min.

Curve B = Blood sugar readings fasting (F) and at 15 and 30 min after the duodenal instillation of 25 gm of glucose in isotonic solution.

Curve C = Blood sugar readings fasting (F) and at 15 and 30 min after the ingestion of 225 cc of 41.7% glucose and simultaneous duodenal instillation of olive oil 60 gtts per min. Total glucose lost from stomach in 30 min = 18.5 gm.

Curve D = Blood sugar readings fasting (F) and at 15 and 30 min after the ingestion of 225 cc of 40.0% glucose and simultaneous duodenal instillation of 0.47% HCl at 80 gtts per min. Total glucose lost from stomach in 30 min = 31.5 gm.

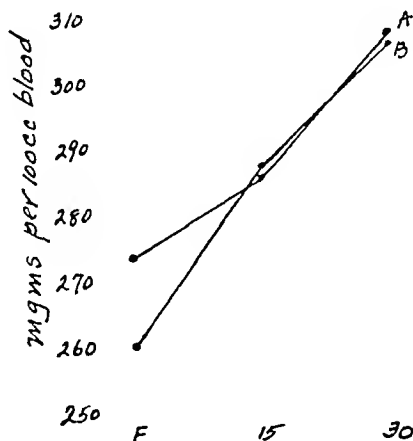


CHART 7

Curve A = Blood sugar readings fasting (F) and at 15 and 30 min after the ingestion of 225 cc of 41.7% glucose and simultaneous duodenal instillation of 0.47% HCl at 80 gtts per min. Total glucose lost from stomach in 30 min = 27.6 gm.

Curve B = Blood sugar readings fasting (F) and at 15 and 30 min after the duodenal instillation of 25 gm of glucose in isotonic solution.

Thus the rise was from 96 mg to 158 mg, a change of 62 mg per 100 c c of blood (curve B). One sees also in this chart (curve C) how much greater is the stimulating action of 0.3 per cent hydrochloric acid. When the 25 grams of glucose in isotonic concentration are made up in 0.3 per cent hydrochloric acid and instilled into the duodenum, the subsequent change in blood sugar is the least in this group of experiments, a change this time from a fasting level of 88 mg to 129 mg, a rise of only 41 mg of glucose per 100 c c of blood.

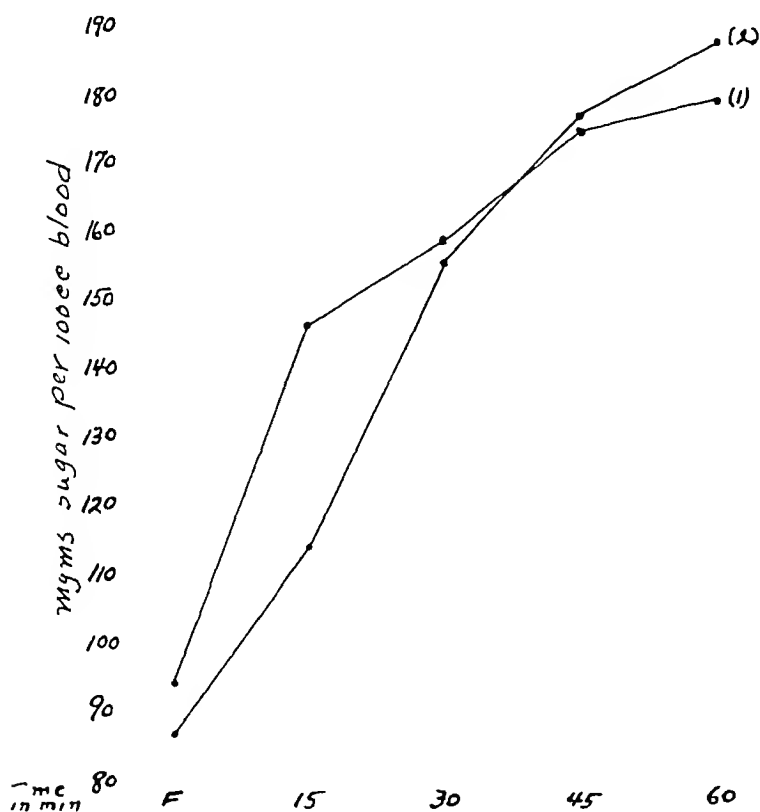


CHART 8

Normal gastric acidity (1) Blood sugar curve after 10 min of adrenalin chloride (1-1000) subcut (2) Same as (1) plus 0.51% HCl intraduodenally 60 gts per min

Chart 3 also strikingly illustrates the difference in action of relatively isotonic glucose and markedly hypertonic solutions. Thus for curve B, 0.47 per cent hydrochloric acid was instilled into the duodenum at the rate of 100 drops per minute, for 15 minutes. The acid was then stopped and 500 c c of 5 per cent glucose rapidly instilled into the duodenum. The blood sugar before the instillation of the glucose was 100 mg per 100 c c. One-half hour after the glucose the blood sugar had risen to 169 mg, a change of 69 mg per 100 c c of blood. The experiment repeated (curve C) with the exception that the 25 grams of glucose were now instilled into the duodenum in a 50 per cent solution, produced a change in blood sugar

concentration in the following half hour of only 6 mg per 100 c c of blood. Chart 3 also indicates that the hypoglycemic action resulting from duodenal stimulation is probably effective only so long as the duodenal stimulant is applied to the mucosa, or at least not after the stimulation is adequately diffused or diluted. Curve A in chart 3 was obtained in the half hour after the ingestion of 225 c c of 38.4 per cent glucose. At the end of the half hour an analysis of the recovered gastric contents indicated that 25.5 grams of glucose had either been absorbed or had entered the duodenum. The blood sugar concentration changed from a fasting level of 100 mg per 100 c c to 188 mg, a rise of 88 mg per 100 c c. In curve B we find that the

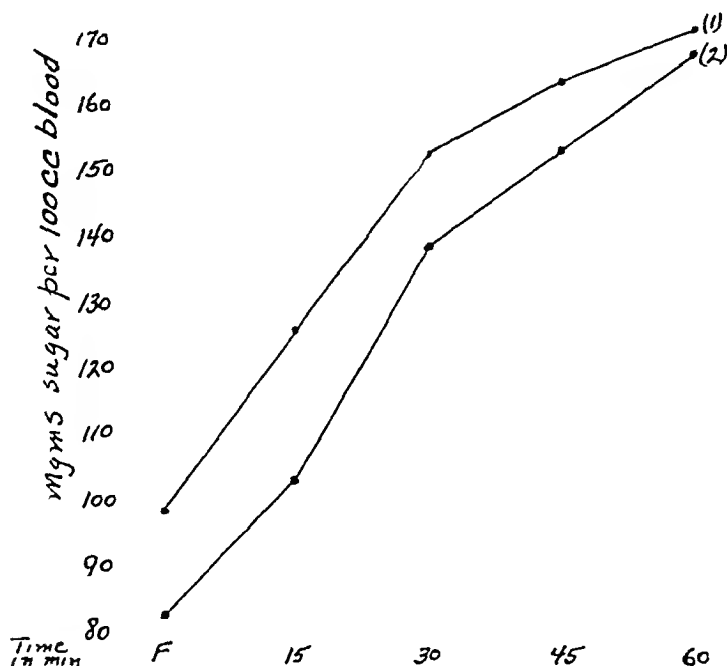


CHART 9

Gastric acidity (1) Blood sugar curve after 10 min of adrenalin chloride (1-1000) subcut (2) Same as (1) plus 0.51% HCl intraduodenally 60 gtts per min

preceding instillation of 0.47 per cent hydrochloric acid had little effect upon the rise of the blood sugar level following the duodenal instillation of 500 c c of 5 per cent glucose, a total amount of glucose comparable to that which had been utilized previously. This is significant when compared with the results recorded for example in chart 1, where the hydrochloric acid action upon the duodenal mucosa was maintained during the period of glucose absorption. In curve B of chart 3, the stimulating effect of the hydrochloric acid upon the duodenal mucosa was rapidly diluted by the introduction of a large amount of relatively isotonic glucose, which in itself has no local stimulating action. Curve C, chart 3, on the other hand, shows a sharply contrasting result even though the same total quantities of

hydrochloric acid and glucose were used. In this instance, however, the stimulating mucosal effect of the hydrochloric acid instead of being dissipated, is if anything, enhanced by the markedly hypertonic glucose solution. We see, therefore, in curve C, a result as definite as if continued duodenal stimulation had been maintained.

SUMMARY

A brief historical survey is furnished of the development of our knowledge of the results of duodenal stimulation beginning in 1825 when Leuret and Lassaigne observed the pancreatic effect of acid applied to the ampulla of Vater in the horse and dog. Various steps led up to the discovery of secretin by Bayliss and Starling. Duodenal extracts were later shown to contain separable hypoglycemic and secretagogic agents. The literature dealing with the nature and mode of action of the hypoglycemic agent is critically analyzed.

Our method for studying this duodenal hypoglycemic mechanism in man derives from earlier studies of the gastric absorption of concentrated glucose solutions. A method is described whereby the effect of duodenal stimulation upon the utilization of the glucose absorbed from the stomach may be determined. The method of determining the effect of such stimulation upon adrenalin hyperglycemia is likewise described.

The data from our own studies appear to indicate the following:

- 1 Glucose, at least when in high concentration, may be absorbed by the human stomach.

- 2 Duodenal stimulation by hydrochloric acid will prevent a rise in blood sugar even though the amounts of sugar absorbed from the stomach would ordinarily raise the blood sugar level.

- 3 The same effect was observed in one diabetic patient but did not occur in another very severe diabetic with a calcified pancreas.

- 4 The prevention or counteraction of alimentary hyperglycemia by duodenal stimulation is shown to be not a function solely of hydrochloric acid. Other agents which could stimulate the duodenal mucosa were equally efficacious. Thus similar results were obtained with fat, hypertonic solutions of sodium chloride and sodium bicarbonate, and of glucose itself.

- 5 While duodenal stimulation could prevent alimentary hyperglycemia, peculiarly enough, it did not carry the depression of glucose concentration below the fasting level. These observations are similar to those of Laugh-ton and Macallum who found that their duodenal extract did not reduce the blood sugar below the normal resting level after induced hyperglycemia.

- 6 Duodenal stimulation did not alter the normal fasting blood sugar level.

- 7 Duodenal stimulation failed to prevent or decrease the hyperglycemia incident to adrenalin chloride injection.

From a study of the literature on the effect of duodenal extracts and their possible method of action, we believe there is adequate evidence to show that their action is not due to secretin or to an insulin extract from the duodenum. It would appear to depend, in the dog, upon a combination of islet stimulation and direct action of a duodenal hormone upon glucose metabolism. From the results reported in the depancreatized animal, the direct action is the essential one. From our data in a severe diabetic, it would seem that, in man, the duodenal mechanism is essentially concerned with islet stimulation. It would seem, therefore, that little could be expected from the use of duodenal extracts in the treatment of diabetes in man. In the mild cases of diabetes there may be some effect from islet stimulation, in severe diabetes there is probably no effect or even an injurious one by stimulation of already severely damaged islets.

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CHRONIC HYPOCHROMIC ANEMIA IN WOMEN

ITS GASTROINTESTINAL, GYNECOLOGIC, ENDOCRINE AND PSYCHIATRIC FEATURES[†]

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So-called *idiopathic hypochromic anemia* has been frequently discussed in the literature. Most authors emphasize the hematological aspects, neglecting other important clinical features presented by patients with hypochromic anemia which seem to us to have an important etiologic bearing. Moreover, failure to take proper cognizance of these conditions in our opinion precludes the possibility of intelligent management. These conclusions are the result of studies which will be reported below. In our opinion, the term *idiopathic* as applied to hypochromic anemia is seldom justified.

The present report is based on an intensive study of 26 women with chronic hypochromic anemia, special emphasis being placed on the gastrointestinal, endocrine, gynecologic and psychiatric problems which these patients presented. Our approach to the problem along these lines was prompted by the frequent presenting complaints of "nervousness" and "indigestion" which are also emphasized in the literature in describing this condition. Our aim was to determine possible organic or functional backgrounds for these symptoms. Gynecologic surveys were, of course, imperative since our series was composed exclusively of women. Endocrine investigations were indicated by the surprising frequency with which symptoms of glandular dysfunction were encountered. Neuro-psychiatric examinations were undertaken to determine the significance of "nervous" complaints. As a group, these patients showed a striking uniformity as to symptoms, blood findings, as well as clinical behavior before and after therapy.

Nationality and Race This group represents various Caucasian nationalities. Jewish patients, although comprising 3.4 per cent of the Harper Hospital Out-Patient Department attendance, are not represented in this series. Curiously enough, also, there were no negroes, although 7.2 per cent of the clinic enrollment is colored. Conclusions as to a racial predisposition are, of course, not suggested from this small series.

Social and Economic Factors All patients of this series represent the low-income class characteristic of dispensary practice during "depression" times.

[†] Received for publication May 17, 1937.

From Harper Hospital and Wayne University College of Medicine, Detroit.

Age The youngest patient in this series was 22 years of age, the oldest 48 years The average age was 38 years

Period of Observation Average 27 3 months

HEMATOLOGIC FEATURES

The hematologic features of the 26 patients studied are summarized in table 1 It is worthy of note that seven, or 30 per cent, of these patients showed a macrocytosis upon admission This morphologic characteristic is found in anemia of long duration, and is also a frequent indication of blood regeneration due to postpartum bleeding, uterine hemorrhage from fibroids, functional uterine bleeding and multiple pregnancy

TABLE I
Hematologic Features

<i>On admission</i>			
Average hgb	51%	Range	33%-69%
Erythrocyte count	3,600,000	Range	2 million to 4 5 million
Average color index	0 7		
Mean diameter of red blood cells—7 7 or over			7 cases—30%
Mean diameter of red blood cells—7 4 to 7 6			8 cases—35%
Mean diameter of red blood cells—7 3 or below			8 cases—35%
Average leukocyte count	6,200	Range	3,250 to 11,000
<i>After treatment</i>			
Average hgb	92 8%	Range	65%-110%
Erythrocyte count	4,660,000	Range	3 5 million to 5 5 million
Average color index	1 0		
Good hematologic response and good clinical response			12 cases—46%
Good hematologic response and fair clinical response			5 cases—19%
Good hematologic response and poor clinical response			8 cases—31%
Poor hematologic response and poor clinical response			1 case — 4%

In the remaining 16 patients, normocytic and microcytic diameters occurred an equal number of times Three of the patients showing microcytosis were sisters All had a typical picture of idiopathic achlorhydric anemia The appellation *idiopathic* applied to the three cases in question or to others in the microcytic group, is hardly justified since disease entities believed to be exciting or contributory causes of the anemic state were associated

Hemopoietic improvement and favorable alteration in the patient's general physical condition were by no means parallel While anti-anemic therapy was uniformly effective, a multiplicity of general complaints persisted during and after hemopoietic recovery When both blood count and general condition responded favorably, iron alone was usually sufficient to cause remission of symptoms, although in a few cases liver or ventriculin was found to be helpful On the other hand, poor or fair clinical results were not due to persistence of the anemia since little difficulty was encountered in restoring blood balance in these cases The group, therefore,

showing indifferent general response created the impression that factors other than anemia were present. Among the most frequently associated conditions retarding full recovery were gastrointestinal disorders, endocrinopathies (particularly thyroid deficiency and entities causing excessive menstruation), and nervous system instability. In order to meet the individual therapeutic requirements of this series of patients, it is obvious that a rather comprehensive regimen had to be adopted. Among the hormones, desiccated thyroid, parathyroid extract, Antutrin-S, Theelin and Pituitrin were employed, dietary adjustment, hydrochloric acid, laxatives and sedatives were necessary to control the gastrointestinal complaints, while snake venom, calcium, dilatation and curettage, and induction of menopause by radiation or surgical procedures were used in an effort to control the gynecologic conditions. Social adjustment was encouraged by appropriate psychotherapeutic methods.

It is evident that anemia is an expression of disease and seldom exists as a solitary clinical entity. It is equally obvious, then, that its corrective measures cannot be restricted to any one specific group of medication. Numerous therapeutic endeavors are required in the comprehensive management of the anemic patient. Hence in planning treatment, this concept should govern the hematologist and clinician.

GASTROINTESTINAL FEATURES

Atrophy of the lingual papillae with the production of a smooth tongue was present in 25 per cent of our cases. An additional 12 per cent complained of burning of the tongue in the absence of atrophy.

The gastric acidity was determined one or more times in each case (see table 2). True achylia, with no response to alcohol ingestion or histamine injection, was present in 54 per cent, false achylia (no free acid after alcohol meal, but present after histamine injection) in 12 per cent, and hypoacidity (free acid 0 to 20) in 15 per cent. Acidity was less than normal, therefore, in 81 per cent of our cases. The crucial role which free hydrochloric acid plays in the digestion and utilization of blood building elements from food has been pointed out by Mettler, Kellogg and Rhinehart¹.

Gastrointestinal symptoms have been repeatedly described in this disease, usually being referred to as "indigestion" or "dyspepsia." An attempt was made to analyze more exactly the nature of the dyspepsia by the use of clinical and roentgenologic methods. Table 2 reveals the gastrointestinal diagnoses made in our series. Seventy-three per cent of the patients had disturbances of colonic function of the type usually referred to as unstable colon (Kantor²) or irritable colon (Jordan and Kiefer³). This condition is marked by pain in any portion of the abdomen, never severe but present over long periods of time, and often accompanied by belching, a

sensation of distention, constipation, diarrhea, or alternating constipation and diarrhea

The digestive symptoms were often the outstanding ones, overshadowing the evidence of anemia. Treatment which raised the blood levels to normal did not as a rule alleviate the dyspepsia. The digestive disorder may also be a cause for failure of treatment or for immediate recurrence of anemia since these patients often choose a bland diet, high in starches and low in meats, vitamins and iron containing vegetables. The caloric intake may also be low because of the distress occasioned by food, and the cathartics frequently taken may interfere with absorption.

TABLE II
Digestive Symptoms

A	Tongue smooth	25%
	Tongue not atrophic but complains of burning	12%
	Tongue not atrophic	63%
B	Gastric acidity	
	True achylia	54%
	(No free acid after alcohol or histamine)	
	Pseudo achylia	12%
	(No free acid after alcohol, free acid present on histamine injection)	
	Hypoacidity	15%
C	(Free acid after alcohol 0° to 20°)	
	Normal acidity (20° to 40°)	15%
	Hyperacidity (40° and over)	4%
	Gastrointestinal diagnoses	
	Irritable colon	19 cases, (73%)
	Constipation, no subjective symptoms	2 cases
	Internal hemorrhoids	4 cases
	Probable cholecystitis	3 cases
	Chronic appendicitis	1 case
	Oxyuris infestation	1 case
	Indigestion, unclassified	1 case
	No gastrointestinal symptoms	3 cases

In addition to colonic disturbances, other gastrointestinal conditions were also present, such as internal hemorrhoids, cholecystitis and oxyuris infestation. Only three patients (12 per cent) did not complain of gastrointestinal symptoms.

Because of the frequent occurrence of irritable colon, our patients were routinely given a diet high in meat and green vegetables, in which the gas producing foods as cabbage, cucumbers, raw apple, fried and spicy foods were eliminated (see anti-anemic diet). Other agents were frequently employed: anti-spasmodics (belladonna), sedatives (bromide or phenobarbital), and mineral oil by mouth, or olive oil by retention enema. The gastrointestinal symptoms were quite satisfactorily controlled by this type of management.

All patients with deficient gastric acidity were given dilute hydrochloric acid. Occasionally a case was noted where the dyspepsia disappeared immediately after the addition of acid therapy.

Following the suggestion of Gray and Wintrobe,⁴ a dietetic history was taken to reveal the food intake during the development of the anemia. The following dietary abnormalities were noted:

Low meat and iron intake	32%
Low calcium intake	49%
Low vitamin A	4%
Low vitamin B and C	36%
High starch intake	44%

These figures are not surprising when one considers that we are dealing here with clinic patients in depression years.

In general, patients on a low meat diet also ate other foods low in iron. About half the patients had a low calcium intake, a situation not peculiar to anemic patients since it has been shown that adults generally have a negative calcium balance, the patients drawing on the reserves of these substances stored in bone.

The low fruit and vegetable intake caused not only a deficiency of iron but also of vitamins B and C. The high starch diet taken by 44 per cent of the patients is common in the average American dietary.

The diet list routinely given to our patients was designed to increase the meat and iron intake, and to provide adequate minerals, vitamins and calories.

ENDOCRINE FEATURES

(a) *Thyroid Function* Thyroid function was determined by clinical signs and symptoms, determination of the basal metabolic rate and by response to thyroid therapy. Results of the survey showed:

Normal thyroid function	12 cases, 48%
Hypothyroidism	12 cases, 48%
Low metabolic rate without hypothyroidism (no data, 1 case)	1 case, 4%

Hypothyroidism was present in about one-half of our patients and was moderate in degree, there being no cases of myxedema. Two patients with hypothyroidism had had previous thyroidectomies. In many, the hypothyroidism would have remained undiscovered unless looked for specifically. Basal metabolic rates were only of corroboratory value, seven of the 12 having rates from 0 to —10, and five from —11 to —20, none were below —20. A single case had a low basal rate (—17 per cent) without clinical hypothyroidism, her condition became worse on the administration of thyroid extract.

Anemia accompanying myxedema is well known and will often respond to thyroid extract where iron therapy is unsuccessful. It is our opinion that minor degrees of hypothyroidism play some role in the production of anemia, perhaps because the rate of iron metabolism is diminished.

Patients with anemia frequently manifest symptoms bearing a marked resemblance to those of hypothyroidism, namely fatigue, dry skin, brittle nails, and abnormal sensitivity to cold weather. A further resemblance is that the basal metabolic rate is said to be lowered in anemia. The clinical survey of the patient for evidences of hypothyroidism was made after the anemia had been wholly or largely corrected by anti-anemic therapy, metabolic rate determinations were again made when the blood had reached a normal or almost normal level. Another criterion for the diagnosis of hypothyroidism was a favorable response to thyroid medication. Demonstration of hypothyroidism was important since clinical improvement resulted from the administration of thyroid extract in patients who were persistently fatigued even after the blood level had been brought back to normal.

OBSTETRICAL AND GYNECOLOGICAL FACTORS

(a) *Menstrual Function* Of the 26 patients, 17 (65 per cent) gave a history of marked menorrhagia. Two (8 per cent) had moderate menorrhagia, and the remaining seven (27 per cent) had menstruated normally. Eight patients had reached or were approaching the menopause, two had artificial menopause induced by us because of excessive vaginal bleeding, one by irradiation, one by surgical measures.

Of the 19 who menstruated profusely, 10 (55 per cent) had normal thyroid function, and 9 (45 per cent) had signs and symptoms of hypothyroidism. It is generally believed that menorrhagia is more commonly associated with hypothyroidism than with hyperthyroidism. One of our patients, however, complained of menorrhagia while hyperthyroidism was present, when hypothyroidism developed after her fourth thyroid operation, menorrhagia persisted to such a degree that artificial menopause was induced by irradiation.

(b) *Multiple Pregnancy* The factor of multiple pregnancy was present in five cases, four patients had had 10 or more pregnancies, and one patient had had six pregnancies within six years.

Pregnancy not only is an important etiologic factor in the anemia but also an important one in causing relapse of anemia in patients who are under control. One patient who had borne eight children before coming under our care had her blood levels brought up to normal, only to relapse in each of the two subsequent pregnancies.

(c) *Gynecological Factors* No organic causes for vaginal bleeding could be demonstrated in the entire group. Five (18 per cent) were subjected to dilatation and curettage to rule out the organic causes for the bleeding. The whole group presented the usual run of minor gynecological pathology such as endocervicitis, trichomonas vaginalis vaginitis, cystocele, atrophic vaginitis. None of these were thought to have any bearing on the vaginal bleeding or anemia.

Other types of endocrine therapy, aside from thyroid extract, were used in nine cases. Theelin was administered to five patients to counteract meno-

pausal symptoms Antuitrin-S was given to two patients to diminish the menstrual flow In one case the periods became more regular, though without diminution in the quantity of blood lost In another, 55 injections of Antuitrin-S (averaging 2 c.c. per injection) were given In addition, she received Theelin, Pitocin, surgical Pituitrin, parathyroid extract, and injections of snake venom, all without effect on the menorrhagia Curettage showed a normal premenstrual endometrium We are considering temporary roentgen-ray castration In several of our patients the menstrual flow became normal after the administration of iron alone

NEURO-PSYCHIATRIC FEATURES

Previous writers have characterized patients with hypochromic anemia as suffering from nervousness, fatigue, and a worrisome disposition In an attempt to classify this nervousness more exactly, our patients received a neuro-psychiatric survey

None of our patients showed objective neurological findings This is in great contrast to our cases of treated pernicious anemia who had many neurological findings though few somatic complaints In the hypochromic group there was a multiplicity of complaints of a widely varying nature

TABLE III
Psychiatric Status

(a) No nervous complaints	5 cases
(b) Complaints proportionate to physical ailments	3 cases
(c) Mild anxiety state	2 cases
(d) Anxiety neurosis	4 cases
(e) Asthenia, hypochondriac type	2 cases
Total with normal personality	16 cases or 64%
Constitutional psychopathic inferiority	6 cases or 24%
Psychasthenia	1 case or 4%
Menopausal psychosis	1 case or 4%
Manic depressive psychosis	1 case or 4%
(No psychiatric survey, 1 case)	

Table 3 shows the status of 25 patients who received psychiatric study This shows that one-fourth of the patients fall into the class of *constitutional psychopathic inferiority* Such persons have difficulty in adjusting themselves to the ordinary problems of life Their inability to adjust results in fixation upon numerous minor physical complaints to which the average individual would give no audience Of the six patients classified as *constitutional psychopathic inferiors*, four were of the hypochondriac type with mental depression and centering of maladjustment on somatic complaints, the remaining two were of the inadequate personality type, with inability to adjust to the ordinary rigors of life and resorting to fixation on somatic complaints as an escape from reality These patients were particularly difficult to treat because they lack insight into their problems

In the group classified as having a normal mentality, there were only five (20 per cent) who had no nervous complaints, three (12 per cent) had nervous complaints which were justified by their physical ailments. The remaining eight cases (32 per cent) with normal personalities had encountered domestic and financial situations during the period of treatment that caused emotional states of the anxiety type.

There were two cases of true psychosis, one of menopausal psychosis with paranoid trends, the other was a patient with manic depressive psychosis who later committed suicide.

The large number of patients with constitutional psychopathic inferiority, and also those with a normal personality but with anxiety neurosis, accounts for the poor clinical response to therapy despite the attainment of normal blood levels.

Only eight patients were free of nervous complaints or had nervous complaints which could be referred directly to the anemia. This group obtained subjective relief as soon as the anemia was corrected.

CAUSES OF THE ANEMIA

Table 4 shows the important etiologic factors in the anemia. As the table indicates, among the common factors are (1) diet deficient in meat and iron, (2) deficient gastric acidity and other gastrointestinal disturb-

TABLE IV
Probable Causes of the Anemia

(a) Deficient meat or iron intake	8 cases, 32%
(b) Deficient acidity	21 cases, 81%
(c) Hypothyroidism	12 cases, 48%
(d) Profuse menorrhagia	17 cases, 65%
(e) Other forms of bleeding	6 cases, 23%
1 Post partum	
1 Post abortive	
4 Hemorrhoidal	
(f) Multiple pregnancy	5 cases, 18%
10 or more pregnancies	4 cases
6 pregnancies in a 6-year period	1 case

ances, (3) hypothyroidism, (4) multiple pregnancy, (5) excessive uterine bleeding or bleeding from other sources. More than one of these factors was present in almost every instance, there being an average of 2.6 causes for each case.

The factor of a chronic defect in alimentary function suggested by Gray and Wintrobe⁴ to explain this type of anemia is included under (2) above, but at present defies measurement.

A comprehensive concept to fuse the multiplicity of factors present in a single case is provided by Haden⁵ when he uses the term *multiple nutritional deficiency disease*, defined as a defect in the intake, absorption and utilization of blood building factors. He also includes increased body need,

such as hypermetabolism in hyperthyroidism, and deficient utilization as in chronic nephritis

DIET FOR PATIENTS WITH ANEMIA

Directions

Include in the diet every day

- 1 Fruits—especially oranges, grapefruit, prunes, apricots, peaches, etc
- 2 Vegetables—at least one cooked and one raw vegetable daily, as spinach, lettuce, beet greens, carrots, etc , and dried vegetables as peas, beans, lentils
- 3 Cereals—preferably whole grain
- 4 Bread—preferably whole grain
- 5 Eggs
- 6 Meats—red meats roast beef, beef steak, beef heart, etc , liver, kidney, sweetbreads, brain or tripe
- 7 Milk—should have at least 1 pint daily

Breakfast

Fruit
Cereal
Eggs
Toast—butter
Milk

Dinner

Red meat or liver
Potato or substitute
Vegetable (cooked)
Salad of vegetable or fruit
Bread—butter
Dessert
Milk

Supper

Choose from
dinner list

Do not include

- 1 Condiments, pickles, relishes
- 2 Fried foods, cakes, pastries
- 3 Cabbage, cucumbers, radishes, onions, raw apples
- 4 No canned or preserved fish

ASSOCIATED DISEASES

In addition to the diseases already mentioned, five patients (19 per cent) had hypertension or cardiac disease, seven (27 per cent) had arthritis or neuritis, and two (8 per cent) had positive blood Wassermann tests. In neither case with a positive serologic test was syphilis thought to be an etiologic factor in the anemia, nor was anti-luetic treatment alone sufficient to correct the anemia. There were no clinical signs of lues in either case. In one the anemia relapsed when the patient discontinued iron therapy, and in the other a hysterectomy was necessary because of repeated menorrhagia.

SUMMARY

1 A group of 26 women with hypochromic anemia was observed over a period of 27 months.

2 The term *idiopathic hypochromic anemia* is not recommended since the following factors occurred so frequently that they were thought to be of etiologic significance: deficient meat and iron intake, deficient gastric acidity and other digestive disturbances, hypothyroidism, multiple pregnancy, menorrhagia and other forms of bleeding.

3 The blood levels rose to normal under anti-anemic therapy although many of the patients continued to complain. Satisfactory clinical improvement was obtained only when a comprehensive program of gastrointestinal, endocrine and psychiatric treatment was instituted in addition to hemopoietic therapy.

4 The "indigestion" so frequently present was found to be due to spastic or irritable colon

5 The "nervousness" was frequently due to an anxiety state, yet 24 per cent were classified as *constitutional psychopathic inferiors*

Thanks are due to the Anemia Laboratory established by Parke Davis & Co., to Mr Emil Schleicher for technical hematologic assistance, to Miss Thelma Larsen for sociologic data, and to Miss Gertrude Henry for dietetic supervision

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FEVER THERAPY IN THE TREATMENT OF ACUTE RHEUMATIC FEVER

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At the Fever Therapy Department of the University of Nebraska 172 arthritis patients have received treatments with the Kettering hypertherm cabinet † Of these 12 were diagnosed as acute rheumatic fever This small group, together with three cases from the University of Colorado, furnish the material for this report ‡

The table gives a summary of the cases, eight of which are described in somewhat greater detail in the text Since our primary interest was the effect of fever therapy upon the course of rheumatic fever we have excluded the frequent borderline cases in which there is often clinical disagreement as to whether the disease is rheumatic fever, atrophic arthritis, or a combination of both This fact accounts for the large number of cardiac lesions in the group The joint manifestations were confined largely to the larger joints and there was no residual joint damage except for one case (P M) In six cases there were recurrent attacks of joint involvement similar to those in which fever therapy was tried

There were eight females and seven males The ages varied from nine to 48 years Ten were febrile on admission to the hospital Eight had leukocyte counts of over 10,000 on admission Three had tonsillectomies in addition to fever therapy In six a diagnosis of mitral stenosis was made, one had a mitral insufficiency, one had a pericarditis, and five had a systolic murmur In none was there any record of noteworthy cardiac decompensation

Since the group is too small to permit of any statistical observations a brief summary of eight cases has been included

CASE REPORTS

Case 1 Mrs A H , aged 40, came to the hospital with rheumatic fever of six weeks' duration She had been partially relieved by salicylates, but still had considerable pain, with swelling of the left knee and ankle There was a rather marked mitral stenosis well compensated She ran a low grade fever up to 101 degrees, the leukocyte count was 10,200 with 74 per cent granulocytes, 1 c c of blood settled

* Received for publication May 3, 1937

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† We are indebted to Dr Charles F Kettering, Director of General Motors Research Department, and Dr Walter M Simpson, Director of the Kettering Institute for Medical Research, Miami Valley Hospital, Dayton, Ohio, for the loan of the Kettering hypertherms used in our studies

‡ We are indebted to Dr F Ebaugh, Dr Clarke H Barnacle, and Dr Jack R Ewalt for the privilege of including the three cases from the Fever Therapy Department of the University of Colorado

Case	Sex	Age	Duration of Attack	Number of Attacks	Heart Lesion	Leuko cytes before Treatment	No Fever Temp	Therapy Total Hours	Leuko cytes after Treatment	1 c c Blood Settled		Remarks
										Before Treatment	After Treatment	
M A W	F	11	1 week	3	Mit sten	11 600	103-4	9	9 800	24 mm -20 mm	24 mm -80 mm	Symptom free Relapse in 2 months
E K	F	38	1 week	4	Mit sten	13 000	103-4 104-5	6 3		24 mm -25 mm	24 mm -60 mm	Symptom free Slight flareup 2 weeks later Gained 30 lbs and symptom free 7 months later
D W	M	22	2 weeks	1	Pericarditis	10 000	103-4	9	9 600	24 mm -23 mm	24 mm -60 mm	Symptom free Murmur gone Weight gain 6 months later
A H	F	40	6½ weeks	2	Mit sten	10 200	103-4 104-5	3 12		24 mm -9 mm	24 mm -65 mm	Pulse slower Symptom free
C S	M	26	8 weeks	3	Mit insuf	6 400	104-5	10	6 200			Symptom free pulse slower No recurrence in 2 years
W M	M	35	2 weeks	1	Mit sten	10 450	104-5	8½	7 900	24 mm -19 mm	24 mm -17 mm	Not much if any relief Tonsilectomy
P M	F	19	18 months	1	Sys murmur	7 000	104-5 103-4	9 39	5 000	24 mm -30 mm	24 mm -150 mm	Slight improvement but still active
B J	M	9	3 weeks	1	Sys murmur Extra systoles		102-3	15				Chorea gone Murmur disappeared Symptom free 7 months later
L L S	F	10	10 weeks	1	Sys murmur Extra systoles	13 400	105-6	31		24 mm -90 mm	12 mm -120 mm	Symptom free No heart murmur 6 months later 21 months later recurrence chorea but no other evidence rheumatic activity
H W	M	11	5 weeks	1	Sys murmur		105-6	46				Chorea and pain gone Murmur disappeared
M B	F	15	6 weeks	1	Mit sten	8 720	105-6	25	7 800	60 mm -60 mm	20 mm -60 mm	Pain free Tonsilectomy
G L McI	F	14	2 weeks	?	Mit sten	13 450	105-6	25	6 900	60 mm -60 mm	18 mm -60 mm	Symptom free
C C E	M	48	2 weeks	1	Sys murmur	14 000	105-6	25	10 400			Symptom free
E L B	M	10	2 weeks	3		7 200	104-5	24				Tonsilectomy salicylates rest no relief Complete relief after fever 21 months later symptom free
L T	F	46	4 months	2			104-5	14		24 mm -150 mm	24 mm -150 mm	Complete relief No recurrence 9 months later

24 mm in 9 minutes. After her first fever treatment her pain subsided, fever lessened, and after five fever treatments of 104 to 105 degrees for three hours each she left the hospital in 21 days, pain and fever free, with 1 cc of blood settling 24 mm in 65 minutes. In the 19 months since dismissal this patient aside from a mild attack of pain one month later has been symptom free.

Case 2 Mr D W, aged 22, was admitted with a history that 12 days prior he had developed red painful joints following a severe sore throat. With large doses of salicylates he was improved but still had a swollen tender left knee, a low grade fever, a small area of consolidation at the base of the left lung posteriorly, and a pericardial friction rub heard best over the base of the heart. One cc of blood settled 24 mm in 23 minutes. He responded only slightly to bed rest and large doses of salicylates. After his first fever treatment he became pain free. He received three treatments of fever at 103 to 104 degrees for three hours each, and on dismissal was pain and fever free. The pericardial rub had disappeared and 1 cc of blood settled 24 mm in 70 minutes. Reexaminations during the following six months have shown no recurrences of symptoms. He has gained weight, the heart is normal in size by orthodiagraph and no murmurs are evident.

Case 3 G L McF, aged 14, was admitted to the hospital two days after developing swollen red knees. She gave a history of frequent sore throats. The present attack of rheumatic fever followed three weeks after a severe upper respiratory infection. She had fever up to 102 degrees, a mild hypochromic type of anemia with 13,400 leukocytes, 72 per cent of which were granulocytes. The sedimentation rate was 60 mm in 60 minutes. She had an early mitral stenosis and painful swollen knees. Two weeks of bed rest in the hospital and large doses of salicylates failed to produce improvement. She was then given fever treatments, receiving five at a temperature of 105 to 106 degrees for five hours each at intervals of approximately four days. Following her first treatment the swelling of the affected joints was markedly decreased and she was able to move her legs freely. After her fifth treatment the pain and joint swelling were completely gone. Her temperature and pulse were normal, the leukocyte count was 9,400 and her blood settled 43 mm in 60 minutes. On reexamination 2½ months later she had been entirely free of pain and fever, her joints were still normal, there was a marked improvement in the cardiac murmur. Electrocardiograph and roentgen-ray of the heart were also normal. Her leukocyte count at this time was 6,900 with 55 per cent leukocytes and her blood settled 18 mm in 60 minutes. This case showed marked improvement in contrast to previous failure with bed rest and salicylates.

Case 4 E L B, aged 40, with a history of a previous attack of inflammatory rheumatism 10 years ago, was admitted two weeks after the onset of the second attack, which involved in succession the left knee, left ankle and left foot. There were redness, swelling and limitation of movement. There was no evidence of heart involvement. His leukocyte count was 7,200, 55 per cent granulocytes, and the blood sedimentation rate was 18 mm in 90 minutes. The pain improved somewhat under rest and salicylates. A tonsillectomy brought no further improvement. Since the joint symptoms persisted fever therapy was tried, six treatments of four hours each at a temperature of 104 to 105 degrees, at weekly intervals. Following his fever treatment the pain and stiffness entirely disappeared and he gained six pounds in weight. He was entirely symptom free and without joint swelling 2½ months later.

Case 5 Dr C S, aged 26, had acute rheumatic fever twice, once nine years ago, and a recurrence eight weeks before entering the hospital. The left foot and both ankles were involved. After seven weeks in bed receiving salicylates he still had a tender swollen right wrist and swollen left foot. There was a definite systolic murmur transmitted to the axilla. The pulse was somewhat rapid and did not slow

down normally after exertion. His leukocyte count was 6,400 with 47 per cent granulocytes, and the blood sedimentation rate was 12 mm in 154 minutes. He was given two treatments of five hours each at 104 to 105 degrees at weekly intervals. Following these treatments the pain and swelling disappeared and he was able to return to his work as an intern. Five months later there had been no recurrence of symptoms. This case was relieved by fever therapy after failure following seven weeks of bed rest and salicylates.

Case 6 M A W, aged 11, school girl, with a first attack of rheumatic fever three years previously, entered the hospital one week after a recurrence. On admission she had a temperature of 102 degrees, a moderately advanced mitral stenosis, a leukocyte count of 11,600 with 87 per cent granulocytes, and blood sedimentation rate of 24 mm in 20 minutes. Both knees were red and swollen. Following three treatments of fever at 103 to 104 degrees for three hours each at four day intervals she became pain and fever free, her pulse became normal and her leukocyte count dropped to 9,800 with 58 per cent granulocytes and a blood sedimentation rate of 24 mm in 80 minutes. This patient felt well until two months later when, following an upper respiratory infection, she had a relapse. This relapse, treated by salicylates, bed rest and supportive measures, required four months to become inactive.

Case 7 B J, aged 9, entered the hospital with a chorea following an attack of acute rheumatic fever which began four months prior to entrance. He was running a low grade fever, there was a slight systolic murmur heard best over the apex and an occasional extra-systole. He received six treatments of fever at 102 to 103 degrees for 2½ hours at five day intervals. He made a rapid recovery. Examination eight months later showed no recurrence of symptoms and disappearance of the heart murmur. This patient entirely recovered from an attack of active rheumatic fever complicated by chorea.

Case 8 C C E, male, aged 48, entered the hospital with a history of painful and swollen joints for three weeks following an upper respiratory infection. The joints of the left arm, right arm and leg had been involved in succession. On admission he was unable to use the right arm or leg because of pain and swelling. The temperature varied from 98.6 to 104.4 degrees. There was a soft systolic murmur at the apex and the pulse was irregular at times. The liver was palpable one finger below the costal margin. His leukocyte count was 14,800 with 78 per cent granulocytes, and the blood sedimentation rate was 33 mm in 60 minutes. The electrocardiograph showed a low voltage in all leads. The heart was normal in size by roentgen-ray. He had had no previous attacks of rheumatic fever. There was improvement following large doses of salicylates and bed rest, but because of persistent joint manifestations he was given fever therapy, receiving five treatments at 105 to 106 degrees for five hours each at intervals of approximately four days. There was marked improvement at once in the joints and at the conclusion of the treatments pain, swelling and stiffness had disappeared. The temperature remained normal. The leukocyte count was 10,400 with 72 per cent granulocytes and his sedimentation rate was unaltered.

GENERAL COMMENT

Of the 15 cases treated by fever therapy, three were complicated by chorea. In the group 13 became symptom free following fever therapy. In all, three had relapses. E K had a slight attack of joint pain lasting a few days, two weeks after her last treatment. She then gained 30 pounds and was still symptom free seven months later. Second, M A W had a

relapse two months after completion of treatment which was purposely treated only with bed rest, supportive measures and salicylates. The attack lasted four months. Third, L. L. S., six months after treatment showed no murmur and no symptoms, but 21 months after treatment had a recurrence of chorea alone without leukocytosis, fever, or increased sedimentation rate. There is still no heart murmur and she is receiving further fever therapy at the present time.

One case (P. M.) showed moderate improvement although there were still rheumatic manifestations three months after fever therapy of 48 hours of fever between 103 to 105 degrees. This is the one case noted previously which showed residual joint damage.

Another case (W. M.) had essentially no improvement. After only 8½ hours of fever at 104 to 105 degrees, he refused further treatments. A tonsillectomy was also done without improvement.

Salicylates were given in 12 cases over periods of six days to seven weeks before fever therapy was tried. Although some relief was obtained, in no case was it complete.

Of the group three had tonsillectomies. One (W. M.) showed no benefit 10 days after tonsillectomy and is also recorded as a failure for fever therapy. Another (E. L. B.) received no relief within 10 days after tonsillectomy but did respond to fever therapy. The third case (M. B.) had received four treatments before the tonsillectomy, which was done as a prophylactic measure.

DISCUSSION

Our results indicate that fever therapy does produce definite symptomatic improvement, usually evident after the first treatment. The results obtained are commensurate with those obtained by Barnacle, Ewalt and Ebaugh¹ in chorea complicated by rheumatic carditis, and with our own unpublished observations in chorea. Sutton and Dodge² have reported five cases of rheumatic fever treated by mechanically induced fever with results similar to our own. In a recent personal communication from Barnacle, Ewalt and Ebaugh,³ the incidence of carditis in their 45 cases of chorea was 42.2 per cent, that is, 19 cases. Of these 19 cases, three showed evidence of mild decompensation and one had a pericardial effusion. Immediately following pyretotherapy seven cases of carditis were considered as recovered, seven were improved, and four unchanged. The case of pericardial effusion responded satisfactorily to fever, the effusion disappeared, and he is now in school and on full activity, 20 months after treatment. Of the 19 cases of carditis 12 have been carefully checked in recent follow-up examinations: six patients showed recovery and are on full activity program, while six are improved. There are other cases which are on full activity but the investigators were unable to check them personally so they

have not included these cases in their follow-up report. They have considered all of the accepted criteria for carditis in making their diagnosis and in arriving at the therapeutic results.

It is important, however, to recognize that individual attacks of rheumatic fever have a well marked tendency to subside spontaneously. On the other hand Bland and Jones⁴ in a study of 1,200 cases of rheumatic fever over a period of 13 years have stressed the persistence of low grade and sub-clinical infection with the periodic appearance of rheumatic manifestations. The tendency of rheumatic heart lesions to progress has been emphasized by many. Rothschild, Kugel and Gross⁵ and others have demonstrated the persistence of Aschoff bodies in cases of rheumatic fever as evidence of protracted activity.

It seems evident that fever therapy does reduce the symptomatic activity of rheumatic fever and probably shortens the duration of the attack. The more interesting point to us is whether or not fever therapy will aid in reducing the number of cases showing subclinical activity. In this connection the table shows that in many of the cases leukocyte counts and sedimentation times become normal after fever therapy. A final determination of this point will require much longer periods of study and a larger group of cases than are available to us at the present time.

The method of producing the fever in the patient is possibly not of great importance. Our experience with the Kettering hypertherm has impressed us with the nicety of control of the temperature and the ease with which the patient can be observed and treated while in the cabinet. In this connection it is interesting to note that Bland and Jones did not produce an activation of a rheumatic process in two cases following physical hyperthermia although activation was produced with typhoid vaccine. In the 15 treated cases in our group there is only one (E. K.) in whom such an activation might have recurred. This occurred two weeks after receiving the last of three treatments at weekly intervals. She received six hours of fever in all and the activation lasted two days. From our experience there would seem to be little danger of reactivating the symptoms.

SUMMARY

1 Fifteen cases of acute rheumatic fever were treated with the Kettering hypertherm cabinet for periods of 8½ to 46 hours with temperatures of 103 to 106 degrees.

2 Thirteen cases received complete relief from joint pain and swelling, three cases had recurrences within 2 weeks to 21 months.

3 The possible bearing of fever therapy on the subclinical activity of rheumatic fever is discussed.

4 Because of the uncertain course of acute rheumatic fever we believe that extended studies will be necessary before final evaluation is possible.

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THE COURSE OF HYPERTENSIVE HEART DISEASE

III SIGNIFICANCE OF BUNDLE-BRANCH BLOCK

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BUNDLE-BRANCH BLOCK is not a frequent electrocardiographic finding Hill¹ reported 41 cases, the first 32 (0.8 per cent) of which occurred in a total of some 4000 consecutive cardiac cases examined electrocardiographically in the Royal Infirmary of Edinburgh White² stated that of 9000 cases with electrocardiograms at the Massachusetts General Hospital during 15 years there were 212 (2.35 per cent) with bundle-branch block During a period of one and one-half years at the Cook County Hospital there were 55 (3.34 per cent) cases of definite bundle-branch block in 1646 cases of organic heart disease³ These reports include cases due to all etiologic causes

This type of block occurs most commonly in patients over middle-age often the subjects of hypertension¹ The analysis of cases of bundle-branch block regardless of the etiologic cause of the underlying heart disease has been the method of choice, but is apparently as confusing as considering all the causes of auricular fibrillation under one heading to arrive at a common prognosis For this reason the present report includes only cases of uncomplicated hypertensive heart disease which showed electrocardiograms diagnostic of bundle-branch block Of the 786 uncomplicated cases of hypertensive heart disease seen over a five year period, 36 (4.58 per cent) had bundle-branch block as a constant electrocardiographic finding It was the next most common graphic abnormality after auricular fibrillation (26 per cent), but only one-sixth as frequent as this arrhythmia in the course of hypertensive heart disease Patients classified as having bundle-branch block had electrocardiograms which showed (1) definite left or right axis deviation, (2) appreciable slurring of the QRS complex with a measurable delay of over 0.1 second, and (3) T-waves pursuing a direction reversed from that of the major QRS complexes in Leads I and III All electrocardiograms showing marked delay and slurring of the QRS complex, but failing to fulfill the other criteria mentioned above, the heterogeneous group known as intraventricular, arborization, or incomplete bundle-branch block, were discarded As to whether to interpret the typical bundle-branch block under the old (classical) or the new terminology, this issue has been omitted My opinion, already expressed in previous writing,⁴ coincides with that of O'Farrell,⁵ who stated that it is doubtful from the clinical viewpoint if anything is to be gained by defining the location of lesions of the bundle with minute exactitude

* Received for publication March 27, 1937

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The age, sex, and race of the 36 patients in this series are noted in table 1. These data agree with all previous studies in that the majority were males (32 or 88.8 per cent) over 50 years of age.

TABLE I
Percentage in the Age Groups

Ages	White				Colored			
	M	F	Total	%	M	F	Total	%
31-40	1	0	1	3.9	1	0	1	12.5
41-50	4	0	4	14.1	0	0	0	0.0
51-60	8	1	9	32.2	2	2	4	50.0
61-70	11	1	12	42.1	2	0	2	25.0
71-74	2	0	2	7.7	1	0	1	12.5
Totals	26	2	28	100.0	6	2	8	100.0
	77.8%				22.2%			

As to the duration of life after the onset of cardiac symptoms, table 2 indicates the percentage of patients who were dead as compared with the known living at the end of each arbitrary period. In a previous study on the course of hypertensive heart disease,⁶ it was noted that approximately

TABLE II
Duration of Disease after Onset of Cardiac Symptoms

Duration	Deceased								Living							
	White				Colored				White				Colored			
	M	F	Total	%	M	F	Total	%	M	F	Total	%	M	F	Total	%
1 Day-6 Months	3	0	3	30.0	3	1	4	66.6	10	0	10	55.6	1	0	1	50.0
7-18 Months	4	0	4	40.0	0	0	0	0.0	2	0	2	11.1	0	1	1	50.0
19 Months-3 Years	3	0	3	30.0	2	0	2	33.4	2	0	2	11.1	0	0	0	0.0
4-6 Years	0	0	0	0.0	0	0	0	0.0	2	0	2	11.1	0	0	0	0.0
7-10 Years	0	0	0	0.0	0	0	0	0.0	0	2	2	11.1	0	0	0	0.0
Totals	10	0	10	100.0	5	1	6	100.0	16	2	18	100.0	1	1	2	100.0

80 per cent of the deceased succumbed within two years after the onset of cardiac symptoms. Of the 16 deaths in this series, 13 of the patients (81 per cent) died within two years after the onset of cardiac symptoms. Four white males, however, were alive four to six years and two white females

seven to ten years after the onset of symptoms. In Graybiel and Sprague's⁷ analysis of 395 cases of bundle-branch block (hypertension given as the etiology in 154), in the entire series of the 85 living the average duration of symptoms was five years and ten months, and of the 222 fatal cases, four years and one month. Their report includes many of the etiological factors of heart disease and electrocardiographic diagnoses omitted from this analysis, which makes comparison difficult.

As to the duration of life after the appearance of congestive heart failure (table 3), 15 (93 per cent) of the 16 deceased patients died within 18 months after the signs of heart failure appeared. This percentage may be

TABLE III

Relation of Duration of Disease after Onset of Congestive Heart Failure in Relation to Discovery of Bundle-Branch Block *

Duration	Deceased								Living							
	White				Colored				White				Colored			
	M	F	Total	%	M	F	Total	%	M	F	Total	%	M	F	Total	%
1 Day-6 Months	7 (6)	0 (0)	7 (6)	70.0 (60.0)	3 (3)	1 (1)	4 (4)	66.6 (66.6)	12 (12)	0 (0)	12 (12)	66.6 (66.6)	1 (1)	0 (0)	1 (1)	50.0 (50.0)
7-18 Months	3 (4)	0 (0)	3 (4)	30.0 (40.0)	1 (2)	0 (0)	1 (2)	16.7 (33.4)	3 (3)	0 (0)	3 (3)	16.6 (16.6)	0 (0)	1 (1)	1 (1)	50.0 (50.0)
19 Months-3 Years	0	0	0	0.0	1	0	1	16.7	0	0	0	0.0	0	0	0	0.0
4-6 Years	0	0	0	0.0	0	0	0	0.0	1 (1)	1 (1)	2 (2)	11.1 (11.1)	0	0	0	0.0
7-10 Years	0	0	0	0.0	0	0	0	0.0	0 (0)	1 (1)	1 (1)	5.7 (5.7)	0	0	0	0.0
Totals	10	0	10	100.0	5	1	6	100.0	16	2	18	100.0	1	1	2	100.0

* Bundle branch block in parentheses

compared with the general course of hypertensive heart disease where 85 per cent of the 170 deceased died within one year after the heart failure occurred.⁶

The duration of life after the detection of the bundle-branch block by graphic means was compared with the duration of life after the appearance of congestive heart failure (table 3, figures in parentheses, bundle-branch block). All of the 16 deceased patients died within 18 months after the block was recorded. Herrick and Smith,⁸ in a report on 35 cases of bundle-branch block, stated that 12 or 57.1 per cent of 21 patients whom they were able to follow died within 18 months. Cowan and Bramwell⁹ reported that 13 or 54.1 per cent of their 24 patients died within 18 months after the block was detected. Sampson and Nagle¹⁰ noted especially the high fatality occurring in cases of bundle-branch block during the first year after the discovery of the lesion, and the remarkable diminution of the case fatality in the groups which survive the initial period. Lewis¹¹ concluded that most of the patients who exhibit this lesion are dead within two years, but some

survive many years so that the prognostic significance of the sign itself is indecisive

There was a close and definite relationship between the congestive heart failure and the bundle-branch block in these patients. This association was first suggested by Cowan and Bramwell⁹ who stated that the presence of the block indicates a definite myocardial lesion, but if unaccompanied by signs of cardiac insufficiency is not necessarily of grave prognostic significance. Kurtz¹² reported six cases of transient bundle-branch block, all with organic heart disease, and in two he stated that it was closely associated with periods of myocardial failure.

TABLE IV
Percentage of Causes of Death in 16 Cases with Bundle Branch Block

Causes of Death	White				Colored			
	M	F	Total	%	M	F	Total	%
Congestive heart failure	10	0	10	100.0	4	1	5	83.3
Spontaneous rupture ascending aorta	0	0	0	0.0	1	0	1	16.7
Totals	10	0	10	100.0	5	1	6	100.0

A survey of the causes of death (table 4) in these patients also brought out this relation of block to failure. Congestive heart failure was the cause of death in 15 (93 per cent) of the 16 deceased patients, all of whom died within 18 months after the onset of the failure and the graphic finding of the block. The exception was the youngest patient, a colored male of 31 years who was decompensated for the two years preceding his sudden death from a spontaneous rupture of the descending aorta. Analysis of the literature further bears out the relation of the heart failure to the bundle-branch block. Ten (83.3 per cent) of Herrick and Smith's⁸ 12 deceased patients died of cardiac failure. Nine (81.8 per cent) of Cowan and Bramwell's⁹ 11 deceased patients with hypertensive heart disease died of congestive heart failure. The important factor in these patients with hypertensive heart disease with bundle-branch block was the congestive failure and not the block, in spite of the fact that the graphic finding was typical and persistent in all cases. The importance of congestive heart failure in relation to hypertension and the heart has been emphasized on two previous occasions^{6, 13}

Those additional pathological findings which are common in hypertensive patients were found to be very infrequent in hypertensive cases with bundle-branch block. Gallop rhythm was present in five (13.8 per cent) of the 36 patients. All five were males, and 18 months after the detection of the bundle-branch block two were alive. Campbell and Suzman¹⁴ cited

the case of a 52-year-old male with cardiac symptoms of six weeks' duration and a blood pressure of 210 mm of Hg systolic and 130 diastolic, who had gallop rhythm and bundle-branch block. Nine months later the gallop and the block both had disappeared. They suggested that the gallop rhythm was due to the bundle-branch block, but my cases neither suggest nor bear out such a relationship.

Auricular fibrillation was present in only two (5.5 per cent) of the 36 patients, both white males, one white male (2.7 per cent) had a cerebral hemorrhage, and another (2.7 per cent) had a coronary occlusion during the course of the disease. Only one patient (2.7 per cent), a white female, had diabetes mellitus, which was of seven years' duration.

COMMENT

The pathogenesis of bundle-branch block in hypertensive heart disease is indefinite. In an extended review of the literature Rosenthal¹⁵ found no discussion of this topic. From his studies he concluded that the degenerative changes which occur in the bundle are explained by an increased tonicity of the small arteries and the arterioles which brings about prestasis and stasis in the precapillaries and capillaries.

There are probably many examples of longevity with bundle-branch block which have not been reported. The Bishops¹⁶ cited the case of a 47 year old woman with a blood pressure of 200 systolic and 105 diastolic who had dyspnea of one year's duration when the block was first recorded. Eleven years later she was still well and still showed the bundle-branch block. Sampson and Nagle¹⁰ reported one patient still in reasonably good health 12 years after the discovery of the lesion. In the present series one woman was alive 10 years after the block was noted.

SUMMARY

Bundle-branch block, graphically noted in the course of hypertensive heart disease, occurred in 36 (4.58 per cent) of 786 patients with this disease. It appeared to have no definite diagnostic or prognostic significance in these patients. The block was considered as only an unusual electrocardiographic finding in hypertensive heart disease, the mechanism of which was not clear. The prognosis of the hypertensive patient with bundle-branch block was that of the underlying heart condition, particularly in relation to the occurrence of congestive failure. Sixteen (44.4 per cent) of the patients died within 18 months after the bundle-branch block was graphically noted, and in all except one the cause of death was the congestive heart failure. There was a very close relationship between the bundle-branch block and the congestive heart failure in the insufficient hypertensive heart.

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THE ASSOCIATION OF ADENO-MYO-SARCOMA OF THE KIDNEY (WILMS TUMOR) WITH ARTERIAL HYPERTENSION *

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THE rôle played by disease of the kidneys in the pathogenesis of arterial hypertension has always enlisted the interest of clinicians. Bright drew attention to the fact that in cases of albuminuria there was frequently found hypertrophy of the heart. Traube and Cohnheim correctly interpreted the cardiac hypertrophy as due to increased blood pressure. The association of arterial hypertension with Bright's disease was thus early established. The nature of the relationship was variously interpreted, but the most widely accepted viewpoint was that the disease of the kidney was primary and that from it arose unknown consequences that brought about an abnormal elevation of the blood pressure.

With the gradual differentiation as an entity of essential hypertension or hyperpiesia, and the acceptance of the fact that in this disease the elevation of blood pressure precedes often by years any detectable renal lesion, a first important step was taken away from the conception of an exclusively renal etiology of high blood pressure. There remained, however, as firmly founded, the relatively constant association of acute and chronic glomerulonephritis with arterial hypertension. The most commonly accepted explanation of this association still is that the kidney damage is the primary event and that the arterial hypertension is secondary. On the other hand, in the last 15 years an important group of investigators of this problem have put forward the hypothesis that the disease which we call glomerulonephritis is in fact a diffuse vascular disease characterized by angiospasm. The arterial hypertension according to this theory is a consequence of widespread arteriolar and capillary constriction due to vascular disease. The renal lesions are likewise a product of vascular disease in the kidney, ischemic according to some authors, or primarily due to damage to glomerular capillaries according to others. Those who have accepted this point of view are therefore of the opinion that the kidney lesions are secondary, both in essential hypertension and in glomerulonephritis, and that in neither condition is kidney damage an essential factor in the pathogenesis of the accompanying hypertension. The more radical opponents of any renal origin of hypertension will not even concede that the kidney damage in such conditions as chronic pyelonephritis and polycystic kidneys gives rise to the arterial hypertension which accompanies these conditions in a significant percentage of the cases.

* Read in part before the Association of American Physicians, Atlantic City, May 1937.
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Such extreme opinions are no longer tenable in view of the developments of the last few years. The earlier failures to produce arterial hypertension experimentally in animals by various types of induced kidney damage have been followed by the development of successful methods. Of these the most dependable is that of Goldblatt¹ which consists essentially of a partial occlusion of the renal arteries by means of special clamps. The elevation of the blood pressure in such animals is of marked degree and may be sustained over months or even years. The removal of the clamps in the earlier stages of the process will result in the subsidence of the blood pressure to normal levels. The well controlled work of Goldblatt has definitely shown that in animals this type of interference with the blood supply of the kidneys will produce an arterial hypertension. Moreover recent careful studies of large series of cases of polycystic kidney and of chronic pyelonephritis have definitely shown that an abnormally elevated blood pressure accompanies these conditions at all ages in a percentage of cases too large to be due to coincidence. Further, in autopsied cases of these conditions no cause for the hypertension, other than the renal lesions, has been found. Since the incidence of the hypertension, especially in the early age groups, is too high to be explainable as a coincidental occurrence of so-called essential hypertension, these studies point strongly towards a renal causation for the hypertension in these primarily renal diseases. However, since the lesions are bilateral there is no opportunity to obtain further evidence through observation of the effects on the arterial hypertension of the surgical removal of the presumably causative lesion.

The existence of a renal form of hypertension in man might be considered finally proved if a renal lesion were discovered in man, whose presence was constantly associated with arterial hypertension and whose surgical removal constantly led to the fall of this pressure to normal levels. In five consecutive cases, in infants and young children of the so-called embryonal adeno-myo-sarcoma of the kidney (Wilms tumor) we have observed the concurrence of arterial hypertension. In two of these cases we were able to observe the effect of operative removal of the tumor and found in each that a marked lowering of the blood pressure occurred and that with recurrence of the growth the blood pressure again rose to higher levels. These observations suggest that through a study of a more extensive series of such cases important evidence as to the existence and the nature of human renal hypertension may be obtained. For this reason the data on these cases are felt worthy of report.

CASE REPORTS

Case 1 J. C., a white female child, aged two years, was admitted to the University Hospital because of a mass in the right abdomen, noted first nine days previously and because of hematuria of 24 hours' duration. The history otherwise was of no significance. On examination the mass was found to fill the right abdomen from the costal margin to the iliac crest. It caused a visible protrusion of the abdominal wall. An intravenous pyelogram showed no filling on the right side.

The blood pressure of this child (figure 1) and of the later cases was determined with a mercury manometer with a 3 inch cuff with due care to record only pressures taken when the child was quiet. Blood pressures are taken routinely on the pediatric service. A pressure of 90 mm systolic and 60 diastolic is considered normal for this age.^{2, 3, 4}

This child's pressure before operation was between 150 mm and 180 mm systolic and the diastolic was consistently over 110 mm. The consistency of the elevation of the pressure is noteworthy. Frequent readings throughout the day were taken but no evidence of abrupt variations nor of paroxysmal elevations was obtained.

Study of the renal function showed a two hour phthalein excretion of 80 per cent the specific gravity in the Mosenthal test ranged between 1.018 and 1.032 the non-protein nitrogen was 21 mg per cent. The hypertension, therefore, bore no relation to faulty renal excretory function.

The heart on physical examination and by teleoroentgenogram was not enlarged and the sounds were normal. The electrocardiogram, however, showed left axis deviation and a deep Q. The retinal arteries showed no change.

Nineteen days after admission an attempt was made to remove the tumor surgically. The greater part of the encapsulated mass occupying the site of the right kidney was taken out, but because of the friability of the tissue and the bleeding encountered a portion had to be left. Within a few days after operation the child showed definite improvement. She was alert, interested in her playthings and took nourishment with good appetite. This period of clinical improvement lasted somewhat over two weeks. Then she began to drift down hill. Palpable evidence of

BLOOD PRESSURE CHART

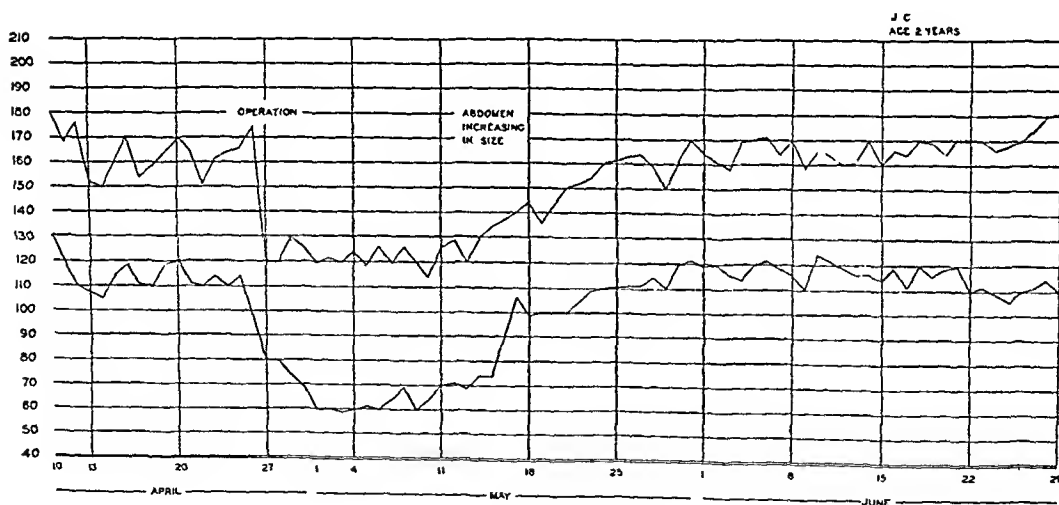


FIG 1 Blood pressure chart in Case 1

recurrence was noted at the end of the third week and by the time death occurred from cachexia and bronchopneumonia, three months after operation, the right abdomen was again filled with a large mass. It may be seen on the chart (figure 1) that following operation during the period of clinical betterment the blood pressure was distinctly lowered, falling to 130 systolic and 100 diastolic, but that as the tumor again increased in size the blood pressure gradually rose and reached its former high level, in a period when the child exhibited marked emaciation and weakness.

The tumor tissue removed at operation weighed 500 gm. Sections (figure 2)

showed numerous epithelial elements arranged in tubular, cystic and glomerulus like structures, embedded in a matrix of myxomatous and spindle cell connective tissue. Muscle fibers were noted in frozen sections. The tumor tissue was very vascular. Large areas of necrosis and of hemorrhagic infiltration were observed. The pathological diagnosis was "A typical embryonal adeno-myo-sarcoma, or Wilms tumor."



FIG 2 Section from tumor mass in Case 1

In an attempt to discover the nature of the pressor action of the tumor, gross serial sections of the mass were carefully studied and numerous blocks taken and sectioned to see whether adrenal medullary or cortical tissue or aberrant chromaffine cells were present. None was found. Moreover, immediate extraction of two samples of fresh tumor tissue was carried out by Dr Wm H Schultz. The pressor effects of these extracts on intravenous injection were tested in young dogs and found to be nil. The extracts gave no color reactions for adrenalin and no adrenalin reaction on intestinal or virginal uterus muscle strip preparations.

An autopsy of this patient showed a massive tumor recurrence weighing 1860 gm. The left kidney and both adrenals were found normal grossly and microscopically. The heart weighed 50 gm which is normal for this age. The larger arteries showed no gross evidence of arteriosclerosis.

Case 2 B C, a colored male child, aged two years, was admitted to the University Hospital in May 1935, because of hematuria of 48 hours' duration. The past history contained nothing significant aside from rather numerous respiratory infections. The child was normally developed for the age. On palpation of the abdomen a globular mass was felt on the right side extending from the costal margin to the crest of the ilium. An intravenous pyelogram showed marked dilatation of the pelvis and calyces of the greatly enlarged right kidney. For four days after admission the patient had a severe hematuria with a considerable total loss of blood.

This child's systolic pressure varied between 120 and 140 mm and the diastolic between 80 and 100 mm (figure 3). This is a well marked though not severe hypertension, when one considers that a pressure of 90 systolic and 60 diastolic is normal.

for this age period This elevation of blood pressure was continuous during the month preceding operation

As in the first child there was no evidence of depression of renal function The phthalein output in two hours on two tests was 65 per cent and 80 per cent The non-protein nitrogen was 26 mg per cent A range of specific gravity between 1 012 and 1 028 was noted

The physical examination of the heart and the teleoroentgenogram did not give evidence of any cardiac enlargement The electrocardiogram did not show left axis deviation and was otherwise also quite normal The retinal arteries showed no changes

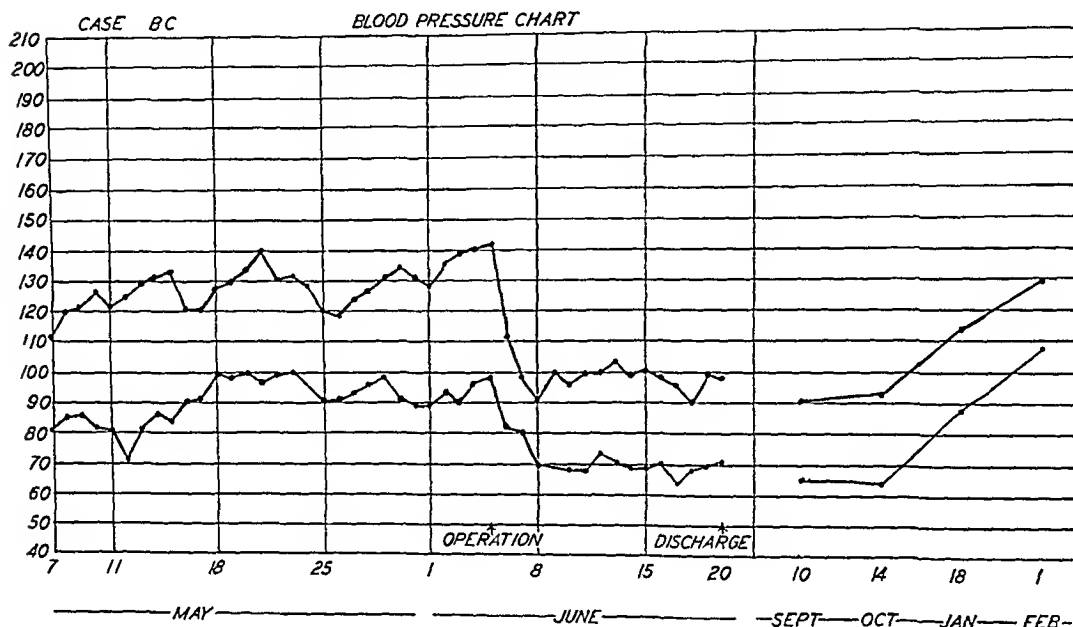


FIG 3 Blood pressure chart in Case 2

One month after admission an operation was performed, a large encapsulated tumor arising from the right kidney was found Kidney and tumor were removed *in toto* (figure 4) The child stood the operation very well, the post-operative healing was uneventful and the child was discharged from the hospital 15 days later Thereafter the patient was seen at intervals in the out-patient department over a period of seven months The blood pressure was normal, 88 systolic and 60 diastolic, until in the sixth month when it began to rise and in the seventh month again reached its former hypertensive level At this last visit a palpable mass was noted at the site of the former tumor Unfortunately, the parents refused to return the child to the hospital, moreover they moved their residence and all attempts to trace this case further were fruitless

The tumor removed at operation from this case was a globular mass replacing the middle section of the right kidney The growth was made up of rather uniform oval or spindle cells, without bundling, but instead rather indiscriminately scattered through a fibrous stroma Hyalinized areas were observed, vascularity was not a prominent feature Only scant adenomatous structures were noted The pathological diagnosis was "A fibrosarcomatous variant of the Wilms tumor"

Case 3 R R, a white male infant, aged two months, was admitted to the Mercy Hospital with the history of increasing abdominal enlargement for one month

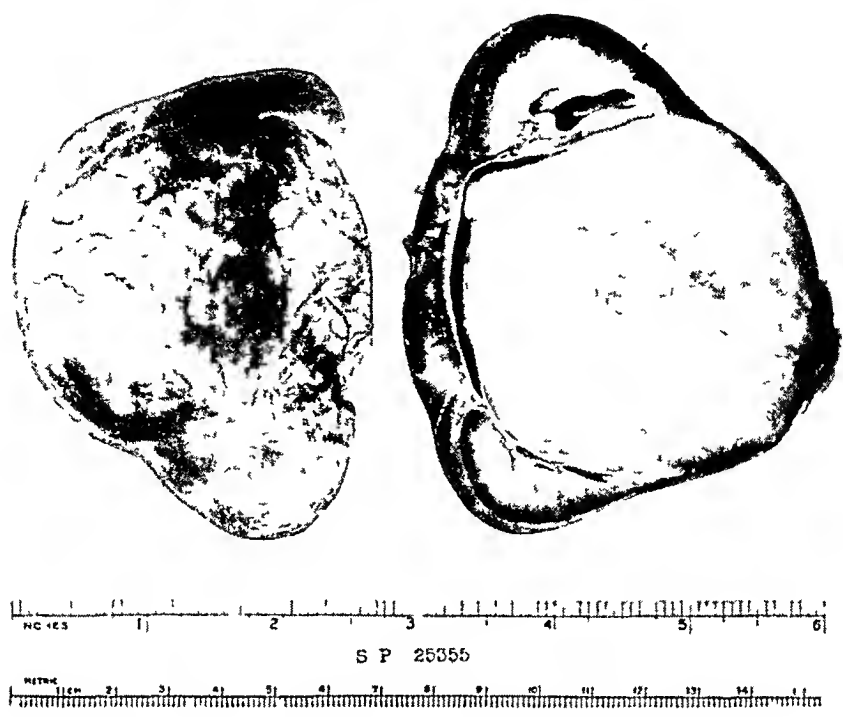


FIG 4 Right kidney containing tumor from Case 2

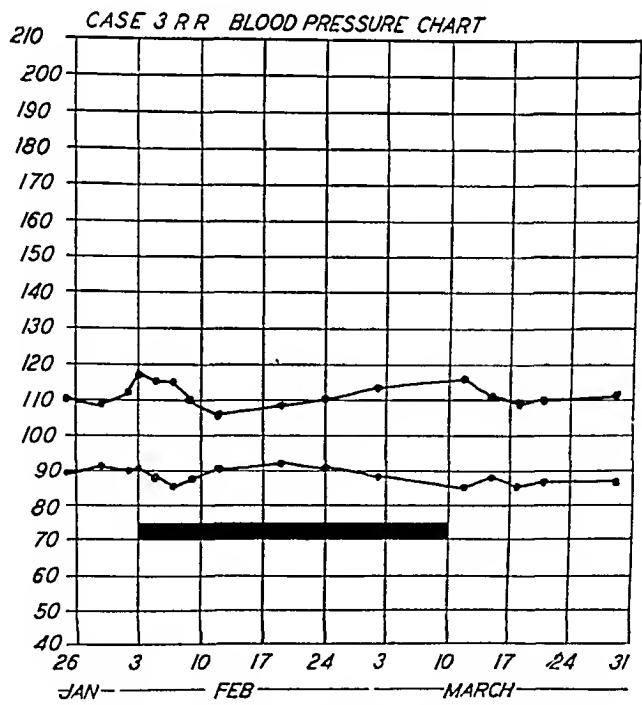


FIG 5 Blood pressure chart in Case 3 The heavy black line indicates the period of roentgen-ray treatment

The child showed marked malnutrition and the greater part of the abdomen was occupied by a large firm mass. The presence of a few red blood cells in the urine and the lack of filling of the right pelvis and ureter on intravenous pyelography indicated that the mass arose from the right kidney.

Sixteen days after admission, through the kindness of Dr. Edgar Friedenwald, one of us was enabled to begin determinations of this child's blood pressure (figure 5). It was found to range between 106 and 116 mm of Hg systolic and between 85 and 90 mm diastolic. The normal mean pressure for this age as determined

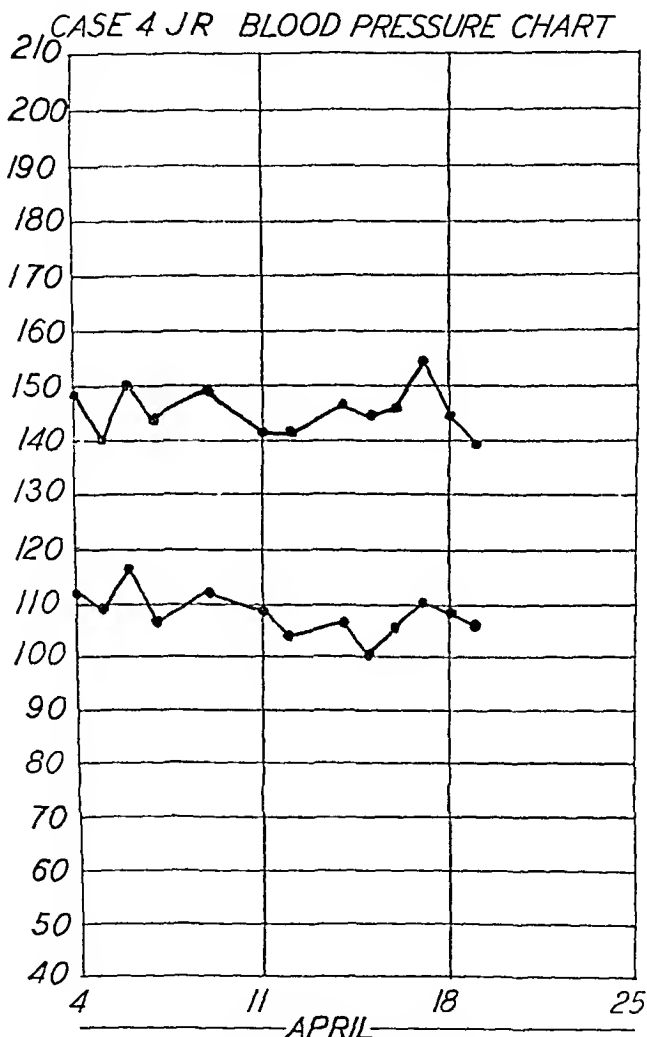


FIG 6 Blood pressure chart in Case 4

in a series of cases (by J. E. B.) is 78 systolic and 56 diastolic. Hence this child's pressure in spite of its cachectic state was elevated to a level corresponding to 150 systolic and 100 diastolic in an adult. The level of the pressure was not affected by a period of irradiation of the growth which very greatly reduced its size. This treatment together with small transfusions was given in preparation for operation but three months after admission the infant was carried off by an acute diarrhea.

At autopsy the remaining mass weighed only 110 gm. The right kidney was almost completely destroyed. The tumor tissue showed marked necrosis, cystic

degeneration and hemorrhagic infiltration. The microscopic sections showed sparse epithelial tubular-like structures in a stroma of spindle cells and myxomatous tissue. The left kidney and both adrenals were normal.

Case 4 J R, a white female child, aged two years, was admitted to the Maryland General Hospital in November 1936, because of a painless enlargement of the abdomen of six weeks' duration. On examination a large nodular mass was found occupying most of the left half of the abdomen. An intravenous pyelogram showed no visualization of the left kidney pelvis. The urine examinations were negative. The non-protein nitrogen was 22 mg per cent. Operation revealed a large tumor of the left kidney which had broken through its capsule in several places. This was removed. Recovery was uneventful. Five months later the patient was readmitted with a large palpable recurrent mass. At this time through the kindness of Dr R P Bay, one of us was able to make repeated determinations of the blood pressure (figure 6). These showed that the systolic pressure ranged consistently between 140 and 150 mm of Hg and the diastolic between 100 and 112 mm.

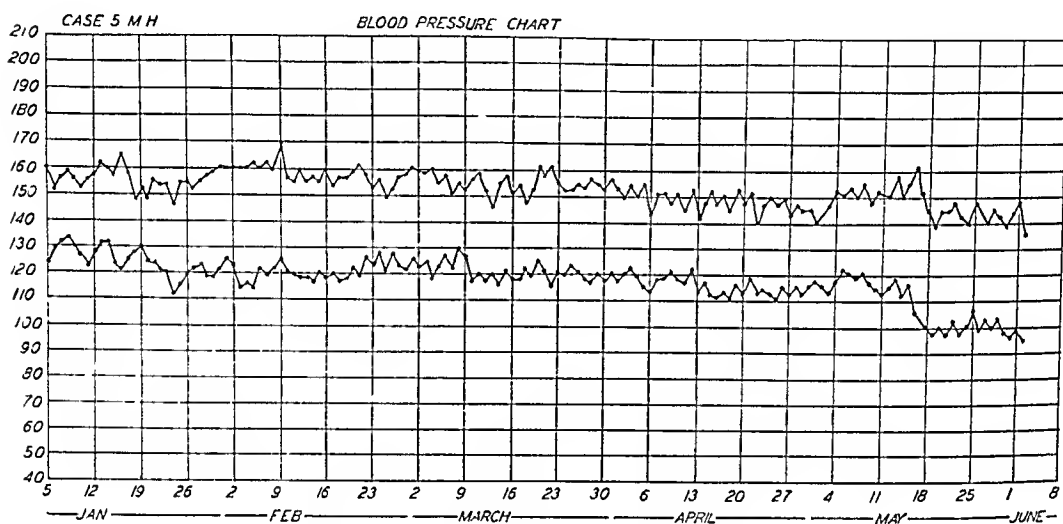


FIG 7 Blood pressure chart in Case 5

The tumor from this patient was partly cystic and partly solid. A gelatinous tissue occupied the cystic area. The more solid tissue contained numerous epithelial elements surrounded by a fibromuscular stroma very characteristic of embryonal adeno-myo-sarcoma or Wilms tumor.

Case 5 M H, a colored male child, six years of age, was admitted to the University Hospital on January 5, 1937 with a complaint of enlargement of the abdomen which had been first noted approximately one year earlier. During this interval vague complaints of abdominal pain of no definite type had been made. Within the two months prior to hospitalization, the abdomen had greatly increased in size. It was stated that constipation had been present since birth and that the child had suffered with occasional respiratory infections. Otherwise the history contained nothing of interest.

On examination the child was well nourished. A mass was palpable in the left flank extending to slightly beyond the midline medially and from the costal margin above, downward almost to the crest of the ileum. It was globular, hard, freely movable, non-sensitive and of even consistency. The edge of the liver extended two fingers-breadth below the costal margin in the nipple line. Both intravenous and

retrograde pyelography failed to show any filling of the left kidney pelvis. The right ureter and kidney pelvis were normal in outline. A clinical impression was that the tumor arose from the left kidney and was probably a Wilms tumor.

The blood pressure in this child on admission was 160 systolic and 124 diastolic (figure 7). The pressure remained consistently elevated throughout the five months' stay of the patient in the hospital. As terminal cachexia set in there was an appreciable decrease in both systolic and diastolic pressures, but, as may be seen from the blood pressure chart, neither ever attained normal levels. The steadiness of the blood pressure level was rather striking for a child of this age. On one occasion readings were made every two hours for sixteen hours (figure 8) and showed very slight variations.

Very numerous urinary examinations in this patient's case failed to show any abnormalities. Concentration tests showed a range of specific gravity between 1.024 and 1.030 on one test and of 1.012 and 1.023 on a second test. The urea clearance was 80 to 87 per cent. The phthalein output was 70 per cent in two hours, the non-protein nitrogen 24 to 32 mg per cent.

Examination of the heart showed clinically no evidence of enlargement, nor change in the rhythm or character of the heart sounds. The electrocardiogram was reported as normal and the teleoroentgenogram showed a normal cardiac outline. The examination of the ocular fundi on admission did not show any vascular changes, but later in the patient's course it was noted that there was some increased tortuosity of the arteries and an increase of the light reflex.

For a period of six weeks after admission the child was treated with roentgen irradiation of the tumor. Nevertheless, during this time the liver increased markedly in size, extending downward into the right flank. The left eye began to show proptosis and vision in this eye was lost. These changes were taken to indicate metastatic growths in the liver and in the left orbit. Roentgen-ray of the skull did not show any bone metastases.

An exploratory laparotomy now revealed a very vascular mass involving the left kidney region and extending across the midline to blend with an ill-defined growth apparently invading both the liver and the right kidney. No tumor tissue was removed.

The subsequent course was entirely downhill with increasing cachexia, increasing enlargement of the abdomen and extension of the orbital metastases downward into the nasal cavity. The child died 151 days after admission. Because of the interest attached to the widespread metastases in this case, complete autopsy findings are appended.

Autopsy June 3, 1937. Pathologist Dr. M. S. Sacks. The body is that of a young negro male child measuring 105 cm in length. It is markedly emaciated. The head and scalp show no changes. There is marked proptosis of the left eyeball. The right eye shows no changes. Examination of the mouth reveals a small cauliflower-like lesion in the hard palate which measures approximately 1 cm in diameter. The chest is emaciated and the abdomen is markedly distended. There is a partially healed left paramedian incision. The external genitalia reveal no change. There is no external lymphadenopathy, jaundice or edema.

The subcutaneous tissue is practically devoid of fat. The musculature of the thorax and abdomen is pale, thin and flabby. On opening the peritoneal cavity there is a gush of clear yellow serous fluid. This is present to the extent of about 200 c.c. The liver is seen to occupy almost the entire upper half of the abdomen. It extends down for a distance of 12 cm below the right midclavicular line. There is a second mass noted in the left flank and as a result of the presence of these masses the entire gastrointestinal tract is pushed downward to the right.

The anterior chest plate is removed and both pleural cavities are seen to be free of fluid or adhesions. The pericardium is smooth and glistening but is somewhat

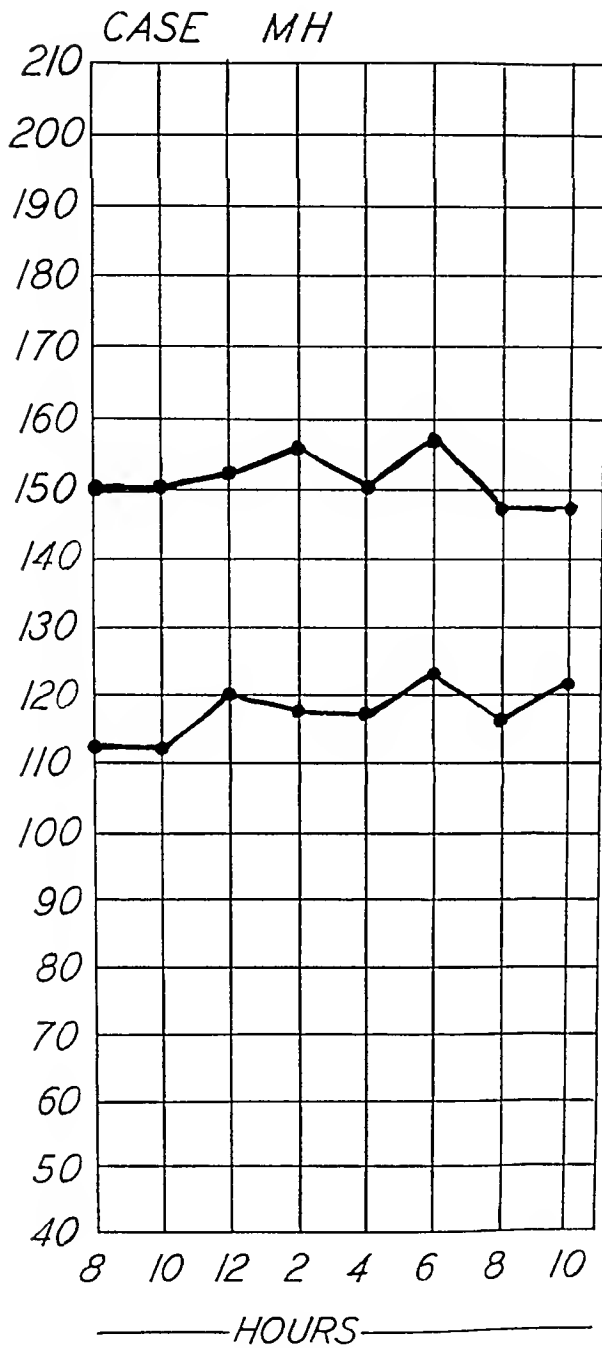


FIG 8 A two-hourly blood pressure chart in Case 5

distended by an excess of clear yellowish serous fluid. The thymus is quite small, it occupies its usual position and reveals no gross changes.

Heart. Weight 110 grams. The epicardium is smooth and glistening. The heart appears to be of normal size. There is some dilatation of the right ventricular cavity. The myocardium has a homogeneous pinkish gray appearance and presents

no gross pathologic change The endocardium both mural and valvular shows no change

Aorta The aorta is small—of normal caliber, very elastic and presents no intimal changes

Lungs Right weighs 250 grams—left 200 grams Both lungs are removed together with the trachea The trachea is patent throughout and examination of its mucosa reveals no pertinent changes The tracheobronchial lymph nodes are found somewhat enlarged, these have a dark red, almost hemorrhagic appearance, they are soft and measure up to 2 cm in length Left lung Examination of the pleural surface reveals it to be glistening but to be studded by multiple nodules of varying size, some of which are sessile and some pedunculated These nodules vary in size up to 5 cm in diameter They are soft and have a pinkish red appearance Some have a distinctly cauliflower-like appearance They are found on all surfaces of the lung On cross section all lobes have a pinkish gray dry appearance and numerous nodules are noted projecting from the cut surface The lobes are distinctly less crepitant than normal The right lung presents an essentially similar appearance One nodule on the pleura of the right lung has a multilocular cystic appearance On puncturing these cysts they are seen to contain air

Liver This organ is tremendously enlarged and weighs 2,700 grams Its contours are markedly distorted by the presence of numerous, roughly circular, metastatic nodules measuring up to 7 cm in diameter These nodules are soft, have a yellowish gray color, with thin red streaks running through them, which tends to give them the appearance of the cut surface of an orange On section it is noted that these masses have displaced the vast majority of the parenchymal cells They have a similar appearance on cut surface The gall-bladder and biliary passages present no gross pathologic change

Kidneys Right weighs 110 grams—left 1,000 grams Right kidney This organ has been markedly compressed and flattened in its anteroposterior diameter by the overlying markedly enlarged liver It can be readily separated from the overlying liver The capsule strips with ease revealing a pale grayish-red smooth surface On cross-section the architecture is seen to be very indistinct The calyces and pelvis are of normal size—smooth and glistening—and show no changes The ureter is patent throughout and of normal size

Left kidney This kidney measures 18 by 12.5 by 7 cm The greater part of the kidney parenchyma has been replaced by a large firm grayish yellow tumor mass At the lower pole may be distinguished a small fragment of pinkish red tissue which bears a resemblance to normal tissue The entire tumor mass and kidney are covered by a dense grayish white capsule The ureter, which is of normal size, may be seen entering at the lower pole of this mass On cross section the cut surface of the tumor has a somewhat lobulated, yellowish-gray, moderately firm appearance At the extreme lower pole may be noted a section of recognizable kidney parenchyma

Adrenals The adrenals occupy their normal position but both are markedly flattened out The right adrenal on section possesses a definitely recognizable cortex and medulla The left adrenal can be separated with ease from the underlying kidney tumor mass and it possesses a grayish-brown homogeneous appearance on cut section, without distinguishable cortex and medulla

Bladder The bladder is small, contracted, empty Examination of its mucosa reveals it to be smooth, gray and glistening

Spleen Weight 70 grams It is firm, the capsule is smooth and taut On section the pulp is dark red The Malpighian bodies may be readily distinguished

Pancreas Weight 30 grams There is no external abnormality and cross section reveals no change from normal

Gastrointestinal Tract The esophagus is patent throughout and reveals no changes. The stomach is contracted. The rugae are prominent but no gross lesions are evident. Examination of the mucosa and wall of the remainder of the intestinal tract reveals no changes until one comes to the descending colon. The wall here is somewhat thicker than normal. The mucosa has an edematous appearance and under the serosa may be noted multiple small petechia-like areas occurring in large numbers.

Lymph Nodes The peripancreatic lymph nodes display a red hemorrhagic appearance, they are somewhat larger than normal. On cross section they present a red granular surface.

Head Not opened.

Anatomical Diagnosis

Embryoma (Wilms tumor) left kidney, with metastases to liver, lungs, parietal and visceral pleurae, palate, left orbit, peri-pancreatic and tracheo-bronchial lymph nodes, proptosis, left eyeball, ascites (200 cc), pulmonary atelectasis, partial, bilateral, partially healed left para-median surgical incision, emaciation, extreme

Microscopic Notes

Heart This section of left ventricular myocardium shows well preserved muscle fibers which are apparently moderately hypertrophied. The epicardium is seen to contain a moderate amount of fat. Cross sections of coronary vessels seen here show no thickening of their walls. There is no scarring or increase in interstitial tissue.

Lungs (two sections) These sections show an air containing tissue. Occasional groups of alveoli are collapsed but these seem to be in proximity to tumor nodules. The interalveolar capillaries are congested. The bronchioles are normal histologically. Scattered throughout the parenchyma and also arising from the visceral layer of pleura are noted fairly numerous nodules composed of neoplastic tissue. The nodules are of varying sizes and display a structure which varies from a densely cellular compact tissue to one composed of loose, anastomosing cords of cells. These nodules are extremely vascular and are composed of cells possessing no distinct cytoplasmic boundaries, which have a small, somewhat vesicular oval nucleus. Such cells form wavy strands of tissue intermingling in all directions. No distinct epithelial elements are present. A very scant, underlying acidophilic stroma is noted in some areas.

Liver Three sections are examined. One shows the uninvolved parenchyma and the other two are portions of the large metastatic nodules. The parenchyma proper displays no disturbances of architecture. The liver cords are perhaps somewhat compressed and there is slight congestion of the central venules. Scattered cells show mild fatty changes. The tumor nodules have a distinctive structure. One sees here narrow, anastomosing bands of cells, with elongated spindle-shaped nuclei often displaying a prominent nucleolus. These bands are separated from each other by a pale, relatively acellular, loose alveolar-like type of tissue. The nodules are quite vascular. They have apparently compressed and destroyed the liver parenchyma previously present.

Spleen This section shows a cellular pulp which is moderately congested. The venous sinuses are patent. Malpighian bodies are numerous and of normal appearance. Some display germinal follicles. No evidences of neoplasm noted.

Pancreas This section reveals evidence of moderate postmortem autolysis affecting the acinar and islet epithelium. No vascular wall thickening is present.

Large Intestine This section shows a well preserved mucosa and no histological changes in the other layers. Several arterioles are observed in the mesentery and none of these shows any marked intimal thickening.

Kidney (a) Left—This section reveals no disturbance of the normal architectural patterns. The glomeruli are numerous. Epithelium of convoluted tubules shows moderate swelling and some granularity of the cytoplasm. No interstitial changes are present. The arterioles display no changes.

(b) Right—This section displays a narrow peripheral strip of kidney parenchyma with several processes extending downward into a tumor mass. The glomeruli are small and compressed and there is a marked increase in interstitial fibrous tissue. Many tubules are obliterated and those remaining are narrowed and compressed. The tumor boundary is well defined. The neoplasm itself shows an abundance of relatively cellular fibrous tissue between the bundles of which are narrow strands of hyperchromatic cells of a similar appearance to those described above. No epithelial elements are present here and the striking thing is the abundance of fibrous tissue.

Adrenals Three sections are studied, representing portions of both adrenals. These sections reveal narrowing of the entire gland which is particularly marked on the left. The narrowing results in giving the glands an appearance of being all cortex. Moderate postmortem autolysis is noted. Several small cortical adenomas are present. No evidence of neoplastic change present.

Lymph Nodes Three sections examined. One displays no neoplastic involvement, but instead shows a markedly congested medullary portion (probably peripancreatic in location). In the other sections neoplastic tissue, chiefly fibrous in nature, has invaded the glandular structure.

ASSAY OF TUMOR TISSUE

Through the kindness of Dr. John C. Krantz, Jr., of the Department of Pharmacology, the following studies were made to determine the presence of adrenaline or of any other pressor substance in the tumor tissue.

Twenty-five grams of fresh tissue representing different portions of the tumor were finely minced, agitated briskly for one-half hour with 100 cc of normal salt solution, strained and centrifuged. The faintly opalescent liquid obtained gave a positive test for adrenaline with the Folin-Cannon-Denis reagent. The intensity of blue corresponded to about a 1×10^{-5} adrenaline. This reaction is not specific for adrenaline. The Vulpian reaction (FeCl_3 , green color—specific for catechol derivatives) was negative. Comessatti reaction (pink with sodium acetate and mercuric chloride) was negative.

Dog—light ether anesthesia—normal carotid B P 150 mm Hg

0.5 cc 1-10 ⁻⁴ adrenaline	20 mm rise in B P
1.0 cc 1-10 ⁻⁵ adrenaline	4 mm rise in B P
1.0 cc tumor extract	no change
2.0 cc tumor extract	no change
5.0 cc tumor extract	no change
5.0 cc tumor extract	no change
5.0 cc tumor extract	no change

The dog's B P was still sensitive to adrenaline

Ten cc of the extract were shaken briskly with activated charcoal (adsorption of histamine, adenosine, adenylic acid and other depressors). The filtrate (5 cc) was twice injected into the same dog—there was no rise in blood pressure.

The animal experiment along with the negative chemical tests indicate the absence of adrenaline in the tumor, and of any pressor substance extractable by slightly acidulated saline solution.

DISCUSSION

The kidney is the most frequent site of neoplastic disease in infancy and childhood^{5,6} and tumors of the kidney account for approximately 25

per cent of all the malignant growths occurring in this period. The commonest renal tumor at this age is a mixed tumor, named from its structure embryonal adeno-myo-sarcoma, but also frequently designated as the Wilms' tumor. Mixer,⁷ in computing the frequency of this tumor, found 41 renal growths in 22,000 admissions to the Children's Hospital in Boston, of which 30 were of the Wilms type. These tumors are, as a rule, encapsulated, oval to globular in shape, solid and variously subdivided into lobules. The tumor formation is usually separated by a layer of fibrous tissue from what is left of the kidney in which it has developed. The kidney tissue is usually atrophied to a greater or lesser extent by pressure but otherwise shows no abnormalities. Microscopically the growths are composed of so many different types of tissue and exhibit such different degrees of differentiation that no single morphological description will apply. In general, it may be stated that they are composed of a mixture of tissues in which are found nonstriated muscle, fibrous and myxomatous connective tissue and complex arrangements of epithelium suggesting glomeruli and tubules. Adipose tissue and cartilage may also be found. The origin of the tumor is undoubtedly from fetal rests. Wilms, Birch-Hirschfeld, Busse, Ewing and others have offered various theories as to their origin, the only resultant agreement being as to the embryonic nature. The tumor is essentially malignant, metastases occurring mainly by the blood stream and usually affecting the liver and lungs, rarely the opposite kidney. Widespread metastases, such as occurred in M. H. (Case 5), are unusual. Since the growth of these tumors is usually asymptomatic, they are, as a rule, quite large when diagnosed. Therapy by irradiation followed by operation is recommended but rarely results in cure.

We have not found in the literature any earlier observations upon the association of arterial hypertension with embryonal adeno-myo-sarcoma. We do not, of course, feel that the constancy of this association can be considered established until a large series of cases has been observed. It seems important that this fact be determined for if the association is a constant one it will become more likely that the tumor tissue itself is the cause of the hypertension, whereas if hypertension is found in only a certain percentage of cases with Wilms' tumor, as is the case in the hypertension of polycystic kidneys, pyelonephritis and urinary back pressure, it will appear more likely that its cause must be sought in some occasional complication of the tumor growth such as disturbances in its arterial supply, necrosis of tumor tissue, etc. Our own endeavors to find a pressor substance in the tumor tissue or the inclusion within it of aberrant chromaffine tissue have given negative results.

The question arises whether the hypertension might be due in these cases to the kidney tissue damaged by pressure from the tumor growth rather than by the tumor tissue itself. In our second case, B. C., the entire kidney

containing the growing tumor was removed surgically (figure 4), nevertheless, the recurrent growth of tumor tissue led to a return of the hypertensive state

That the hypertension in these cases was in some way a consequence of the tumor growth seems to us a reasonable conclusion from the facts presented. In the first place, the possibility that the association of the two conditions was an accidental one must be considered very remote. Hypertension in infancy^{8, 9, 10, 11} is quite a rarity and when found has usually been accompanied by glomerulonephritis or chronic pyelonephritis or in isolated cases by adrenal medullary tumors, brain tumors or coarctation of the aorta. In our cases, no evidence of nephritis was present in life, renal function was unimpaired and in three cases at autopsy the remaining kidney was histologically normal. In these three autopsied cases likewise the adrenals showed no abnormality. There was no evidence of urinary back pressure. In two cases the aorta was examined and found normal. There was no evidence to suggest an intracranial lesion. In brief, then, complete examination in three cases and such data as we possess on the other two do not afford any other explanation than the tumor for the hypertension.

Moreover, in two cases the removal of the tumor was followed by a significant fall in blood pressure. In the second case, in which the removal was apparently complete, the blood pressure fell to normal levels and remained there for some months. Finally in both of these cases recurrence of the tumor growth was accompanied by a return of the hypertensive state.

It is of particular interest, we feel, that a unilateral renal lesion should cause elevation of blood pressure. In experimental hypertension a permanent elevation has rarely been obtained except when both kidneys have been damaged. It is of interest also that the level of the elevated blood pressure is quite steadily maintained.

We feel that the tumor tissue in these renal tumors has a property possessed by renal tissue when it has been altered by certain types of damage—that is, the property of causing, through as yet unknown mechanisms, an abnormal elevation of arterial pressure. These observations of the relation of these renal tumors to hypertension furnish new support to the view that there are clinical forms of high blood pressure of primary renal causation.

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MEDICAL SHRINES

Remarks at the Annual Banquet of the American College of Physicians
1937

By LOGAN CLENDENING, M D , F A C P , *Kansas City, Missouri*

TONIGHT it is my purpose to discuss with you some memories of our past—the past of medical science and of medical service. Specifically, I want to discuss the memorials of the men and institutions that made that past—memorials in the form of hospital or university buildings, or in the form of statues of the great men and women of our tradition, their birth houses appropriately marked, or their graves properly inscribed.

And I want to suggest that it is a function of this College to encourage the memorialization of our American medical shrines. In our restless and changing country the dwellings and haunts of our pioneer physicians disappear, and all relics and reminiscences of them become scattered or lost. Do we not owe it to them at least to collect their records while those who can recall the past are still here to help us?

Do not be alarmed! I do not intend to desecrate the post-prandial ruminative mood which sits so becomingly on your genial countenances, my learned fellows, by suggesting a subscription. All I ask is your moral support of the work of the local profession, whose duty it should be to do this work in each community. And moral support is a commodity easy to donate, even in the after-dinner glow.

For the past decade and a half, I have spent a considerable portion of my life wandering over the face of the earth seeking out and studying these memorials. They are not always easy to find. They are not usually regular objects of sightseeing, nor frequently given prominence in the guide books. Statues of generals and kings and lawyers there are, as you know, aplenty. Physicians and scientists are hard to find. But there comes a peculiar satisfaction when you do find one. It is possible for mankind to remember gratefully the events that really contributed to civilization as well as battles.

For instance, I was walking a year or two ago in the majestic old eighteenth century city of Bath, around the Circus that once was and still is a fashionable crescent of residences. I had noticed a small plate affixed to one door which announced that this house was once the residence of Richard Brinsley Sheridan, so I became interested in reading these notices. Suddenly I found myself peering at a silver plate which marked the home of Caleb Hillier Parry, 1756–1822. How many visitors to that Athens of the West would know of the achievements of “the distinguished old Bath physician,” as Osler called him, he who described the combination of

* Read at the St. Louis Meeting of the American College of Physicians, April 22, 1937

exophthalmos, goiter and tachycardia, he who was the friend of Jenner, to whom the *Inquiry* is dedicated? And yet to those of us who do know the man, the thought that someone had the pride and took the trouble to point out his earthly residence, is moving and warming

Various communities differ somewhat in their feelings towards their illustrious dead. Last year I determined to visit Berkeley in Gloucestershire, the birthplace and the scene of the labors of Edward Jenner. We established ourselves at Bath as headquarters for the trip and the word "established" bid fair to be very accurate. We were greeted on our first day with a steady, grim downpour of rain. And such wet rain—you could hardly cross the street without being drenched. We stayed in our room with a fire of channel coal (sixpence extra a day) and we stayed there for several days while the weather gave an example of what it could really do to be nasty. At last a morning of semi-sunshine gulled us into taking the bus for Bristol. A fine drizzle greeted my attempts to find the birth house of Richard Bright, and by the time we had seated ourselves in the Gloucester bus the landscape was awash again. At Berkeley it did threaten to clear and remembering the traditions of the excellent cuisine enjoyed by that convivial medical society of which Jenner was the moving spirit when it met at the Berkeley Arms, I ordered lunch and inquired the way to the local mementoes of Jenner. The landlady looked blank and asked me to repeat the name. I did so, adding the information that he had introduced vaccination against smallpox. She said she thought he was dead. I replied that I feared so, too, but would like to see his grave, or statue, or house. She said she didn't hold with vaccination herself but there was a stable boy who specialized in such matters.

While I awaited the arrival of the learned stable boy, I asked for a guide book. A pamphlet on Berkeley was procured, most of the contents of which were devoted to a description of Berkeley Castle, the seat of the Earls of Berkeley, and the principal distinction of which is that it contains a dungeon where the first Prince of Wales starved to death. There was also a brief account of Jenner, referring to his grave in the chancel of the church. The learned stable boy having arrived, would not commit himself to any definite information but ventured the remark that "Vicar would know" and conducted us to the bottom of a lane whence we could see the Church of St. Mary's and the vicarage.

As nearly as I could understand, I was told that the Vicar was away birdnesting. This was finely in the tradition of Jenner's paper on the cuckoo, but considering the weather, seemed to be carrying a tradition somewhat too far. By wandering around I suddenly came face to face with the thatched cottage where Jenner took the lymph from the hand of Sarah Nelmes to inoculate James Phipps. I recognized it from the model reproduction in Burroughs, Wellcome's exhibit at the Chicago Century of Progress Exposition, and it is well I had been there because no plaque or plate or notice indicates why this fragile structure is preserved or what happened

there By Sherlockian cunning, we found the tomb It is marked simply "Edward Jenner" and his dates I liked that, but nowhere else in Berkeley is his name seen, there is not a statue or a tablet or a stone to one of the greatest Englishmen who ever lived

We returned for lunch, but alas for the enthusiasms of biographers when they describe their hero's meals The dining room at the Berkeley Arms was as cold as an enthusiastic New England audience The napkins were heavy with the damp chill of mortality The soup reminded us of the Irish famine victim's complaint about the relief kitchen, which Stokes liked to recite—"Soup, is it? Shure 'tis nothing but a quart of water biled down to a pint to make it sthronger" There was a piece of fish of the whiteness of virgin snow, which had been boiled until every vestige of animation had long since departed, and by its side with a thick white sauce, over the surface of which the congealing process of coagulation had done its deadly work That sauce tempted me and while the waiter was out of the room I inserted my clinical thermometer into its center I record as a solemn fact that the temperature was exactly 54 degrees Fahrenheit

Do not mistake me I admire the English And the thing I admire most about them is their ability to live in England And, furthermore, to me the greatest Englishmen who ever lived are those great and great-great-grandparents of mine who left England and settled in this land of furnaces and bathtubs, of sunshine and shad roe, of ice and mint, of cheap cigars and good coffee, and silk hats only on formal occasions

I had a Scotch hughball for dessert at the Berkeley Arms and then found there was no bus to Gloucester until morning But no enticement would induce me to try the sheets after sampling the napkins and I hired a car from the garage (Hired? We nearly bought it) and set off Then the heavens really opened The vale of Gloucester may be as beautiful as the Cotswald poets say, but for me it is a vale of tears In Gloucester Cathedral there is a figure of Jenner and a window dedicated jointly to him and his friend and biographer, John Baron

I thought on my journey home that someone should begin an agitation for a memorial in his own home for Jenner But then a restraining thought cooled me off Perhaps they don't want it One would have to approach the Vicar of St Mary's first Perhaps it would be better to turn the project over to an organized body—the College of Physicians and the British Medical Association

By contrast is a visit I paid in Italy to Arezzo and asked the hotel proprietor where Francesco Redi lived His face lit up He took me by the arm He said something to the cafe loungers and they accompanied us excitedly into the street The priest joined us I was conducted to the Via Redi and directed towards the villa Soon I stood before two lovely old gates and passed up through the rows of cultivated plants until I stood at the entrance of a fine manor house There a marble plate proclaimed

Qui Nacque E Abito
 Francesco Redi
 Insigne Letterato E Poeta
 Sommo Nella Medicina
 E Nelle Scienze Naturali

One could easily imagine as one stood looking over that peaceful farm how naturally the lord of the manor would turn to those studies in insects and spontaneous generation that made him sommo in medicina et scienze naturali

A soft voice behind me said something, and I turned to find a woman dressed, almost shabbily, in that severe black dress which Italian women affect. She had a shawl over her head and looked almost like one you used to see at Ellis Island. Yet what she said was that he was an ancestor of hers and she graciously conducted me to the chapel where all the Redis, save, apparently, Francesco himself, are buried.

I do not say that this treatment is typical of the English and Italian attitude towards their great dead, but it suggests a lesson to us.

What of the condition of our American medical shrines? I suppose there would be a very general agreement that the most important American contributions to medicine were, first, the introduction of general surgical anesthesia, second, the foundation of the physiology of gastric digestion, third, the establishment of successful ovariectomy, fourth, the suggestion of the contagiousness of puerperal fever, fifth, the discovery of replacement therapy for diabetes, and, sixth, the discovery of specific replacement therapy for primary anemia. Of equal importance as shrines of service are those institutions which have continuously, from their establishment, rendered such distinguished service to our people—our first hospitals, Pennsylvania and Bellevue, and the Surgeon-General's Library.

The South and the North share the honors of anesthesia. The Massachusetts General Hospital, as you know, keeps alive the memory of that dramatic morning of October 16, 1846. At Jefferson, Georgia, Long is represented by a granite shaft.

I have not been to Mackinac Island for many years and am indebted to Dr. Carl S. Cook of Mackinac Island and Dr. A. C. Tiffany of Mackinaw City, Michigan, for the following information:

"Alexis St. Martin was shot June 6, 1822 in the basement of what is now the Early residence at the foot of the hill leading up to this old fort. This building is still in excellent repair but gables have since been built out on the second floor. Dr. Beaumont first attended St. Martin in this basement, but immediately moved him up to the hospital at the fort. This hospital is a small one-story frame building within the fort walls. It was used as the Post Hospital until 1858 when the Surgeon's Hospital was built because of need for more room. Beaumont's hospital was then used as the

quartermaster's store until the final evacuation of the fort in 1895. From then it stood vacant until 1923 when it was rehabilitated and restored as an emergency hospital. An organization of Mackinac Island people and summer residents has equipped the old building with the necessary surgical appliances and it is now used for surgical emergencies. The present operating room is in the old part of the building, and the entire building has been refinished. The hospital is now kept up by gifts made by summer visitors. It is called Beaumont Emergency Hospital.

"There is no plaque marking Beaumont's home, but according to Meyer's book on the life of Beaumont he lived in the east quarters of the Stone Barracks, still standing.

"In 1900 a monument was erected to honor Dr. Beaumont. This was presented by the Upper Peninsula and the Michigan State Medical Societies. This monument is placed just within the Fort walls facing the Straits of Mackinac."

The inscription on the monument says, "Near this spot Dr. William Beaumont, U. S. A., made those experiments upon St. Martin which brought fame to himself and honor to American medicine. Erected by the Upper Peninsula and Michigan State Medical Societies June 10, 1900."

Our city of St. Louis here where we meet tonight, was, for many years, the home of Dr. Beaumont, but Missouri is neither the site of his birthplace nor the locale of those labors which made him famous. His birthplace in Lebanon, Connecticut, is the site of a stone shaft, dedicated on June 29, 1926.

The third spot of first rate importance as an American medical shrine is Danville, Kentucky, where Ephraim McDowell performed the first successful ovariectomy. In 1879, the Kentucky State Medical Society rescued the graves of Dr. McDowell and his wife from imminent dissolution and erected monuments over them. On this occasion Dr. Samuel D. Gross of Philadelphia delivered the oration and Dr. Lewis S. McMurtry, afterwards president of the American Medical Association, accepted the gift in the name of the Kentucky State Medical Society.

Dr. McDowell's property—his residence and office, where this classic operation was performed—was for many years badly neglected, although not because of lack of effort on the part of the Kentucky State Medical Society and other interested organizations.

Dr. Schachner, one of the biographers of McDowell, tells of visiting the house while it was a negro boarding house and as he was going upstairs the landlady pulled off a piece of lath from the disintegrating plaster wall and handed it to him as a souvenir.

Within recent years it has been possible for the McDowell Memorial Committee of the Kentucky State Medical Association to acquire this building, and when I was there last fall it was in process of repair and reconstruction. In the course of the research work necessary to secure the plans for

the restoration, the fact was uncovered that the adjoining property, which is also in good condition, was McDowell's Doctor Shop and Apothecary. The committee is trying to raise sufficient funds to purchase this property, which will cost \$3,000 00, so that the entire McDowell block may be restored. For this work one of our guests at this convocation, Dr. Irvin Abell, has been so largely responsible that it is a pleasure to record our indebtedness to him.

The locale of Holmes' work on puerperal fever is indefinite. And there is no special single institution where Whipple, Minot and Murphy's work on liver in Addisonian anemia was completed. But with this, as with Toronto's honorable shrine of insulin, we can afford to wait a long time before it will be appropriate to memorialize them.

These are our proudest memories, but there are others, hardly less epochal ones. It is appropriate to my subject tonight, since Dr. Bradley is our president, to recall that in that part of Kentucky near Danville, that beautiful fertile region of the blue grass of Kentucky, there is, in Dr. Bradley's own city of Lexington, the site of the first medical college west of the Alleghenies and the fifth in the United States, Transylvania College.

The medical faculty no longer functions in Lexington, but there is a reminder of this early center of medical education still intact. Early in the nineteenth century the trustees raised a considerable sum and sent Charles Caldwell, Professor of Medicine, to Paris to purchase a library. "The time of my arrival in Paris," he wrote, "was uncommonly propitious for my purpose. The wastelays of the French Revolution had not entirely passed away. The libraries of many wealthy persons had found their way to the shelves of the bookseller. I found and purchased at reduced prices no inconsiderable number of the choicest works of the fathers of medicine from Hippocrates to the revival of letters." These books are still in the general library building of the University—a beautiful and typical collection of an eighteenth century physician's books. They cry out for proper housing.

From this area of Western Kentucky as a center, there came the pioneer medical profession of this part of the world—of Cincinnati, St. Louis and Missouri. Since we are meeting on the very ground which was the hub of the settlement of this western territory, may I venture to recall to you some recollection of the life and experience of our pioneer Missouri physicians?

I have here in my hand a little book, one of the rarest examples of Americana, which is entitled SAPPINGTON ON FEVERS. It was printed at Arrow Rock, Missouri, in 1844.

Those of you (naturally I address particularly the Missouri part of our audience) who have visited Arrow Rock, which is about midway between St. Louis and Kansas City in a beautiful rolling countryside reminiscent of the blue grass region of Kentucky, will remember the old Arrow Rock



FIG 1 John Sappington From the portrait by George Caleb Bingham

Tavern which was close to the home of John Sappington, and which now exhibits a museum of his case books, saddle bags and other relics

John Sappington was born in Maryland in 1776 His father joined the tide of western emigration and moved to Tennessee, settling in Nashville John Sappington studied with his father as preceptor and later was associated with him in practice in Nashville In 1814 he rode to Philadelphia on horseback, where he attended for one year, from 1814 to 1815, a course of medical lectures and received a diploma from the University of Penn-

sylvania He heard the arguments for and against the violently depletive treatments that the followers of Rush and Cullen taught and practiced in the treatment of fevers Returning to Tennessee, he emigrated in 1817 to Missouri and located in what was then the western frontier settlement of Howard County Two years later he moved across the river and settled in Saline County, near Arrow Rock

The medical problems of this territory were quite as grave as any other danger to which the settlers were exposed There was a well defined sickly season, starting in July and extending into September until the first frost Fever and chills were nearly universal visitations and the farmers expected so much incapacitation at this time that they made particular efforts to have their crops and other important matters attended to before the onset of the sickly season



FIG 2 The Tavern at Arrow Rock, Missouri It houses many Sappington relics

The cause of these fevers and agues was unknown Daniel Drake writing in 1830, says "There is a noxious gas given out throughout the great Mississippi Valley system which affects the people of the west and south" This noxious gas theory is the one which gave malaria (mal air) its name Drake afterwards discarded this noxious gas theory

In Morse's "Western Gazeteer" in 1810, in regard to Louisville, Kentucky, it is said that "its unhealthiness due to stagnating waters back of the town has considerably retarded its growth"

Early settlements in Howard and Saline Counties, Missouri, were frequently abandoned due to the prevalence of shaking agues

It is to the credit of Dr John Sappington, and it is the merit which has given his book permanent value, that he early recognized the specific therapeutic nature of quinine in these autumnal Valley fevers. Let me emphasize that it was quinine on which he relied. Daniel Drake preferred, in many cases, Peruvian bark to quinine but Sappington wrote "The names of Pelletier and Caventou, who first separated the pure alkaline salt, called quinine, from the bulky and inert mass in which nature had placed it, deserve to be remembered with gratitude by all mankind."

In this particular community, contiguous to our meeting place tonight, Sappington's influence was very strong. It is not too much to say that his advocacy, in season and out, of the virtues of quinine did much to make this section a healthy place of residence.



FIG 3 Dr Sappington's grave in the family cemetery at Arrow Rock. In this same cemetery are buried two governors of Missouri, C F Jackson and M Marmaduke.

He had by no means an easy time of it. His few professional brethren had been strongly imbued with the virtues of the depleting system of Rush, under whom many of them had sat. He probably shared, as Dr Thomas B Hall suggests, Oliver Wendell Holmes' opinion of Rush's epigram, "Medicine is my wife and Science my mistress," of which Holmes said, "I do not think that the breach of the Seventh Commandment can be shown to have been of advantage to the legitimate owner of his affection."

Even so fair minded an inquirer as Dr Daniel Drake was unimpressed by Sappington's ideas. Drake was a great influence all over the Mississippi Valley in those early days.

His "Western Journal of the Medical and Physical Sciences" was a source of light and comfort to physicians all over the West. At a time when the companionship and advice of fellow physicians was keenly missed on account of the sparsely settled land, the pioneer physician found in this journal both accounts of medical progress in the great centers of the world and also accounts of the local diseases of his own territory—new, strange and largely unrecorded in textbooks.

These accounts came largely from the pen of Drake himself and were the basis for his really major contribution to medical science—his “Prin-

THE
THEORY AND TREATMENT
OF
FEVERS,

BY
DR. JOHN SAPPINGTON,

SALINE COUNTY, MISSOURI.

REVISED AND CORRECTED
BY FERDINANDO STITH, M D ,
FRANKLIN, TENNESSEE.

*A Faul may plant, an Apollos may water, but the increase is of God —First
Epist Paul to the Cor., Chap 3d, 6th verse.*

ARROW ROCK
PUBLISHED BY THE AUTHOR.

1844.

FIG 4 Title page of Sappington on Fevers

cipal Diseases of the Interior Valley of North America” (1850) To collect material for this, Drake traveled restlessly up and down all our river valleys He visited Arrow Rock, Missouri, some time about 1835–1840, probably because he had heard of the fame of Dr John Sappington and his treatment of autumnal fevers Sappington condemned the depleting treatment of purging, vomiting and bleeding, because all that is necessary to effect a cure is quinine, “one grain every two hours, day and night”

Drake records (p 170, Interior Valley) a visit to Arrow Rock and a conversation with Dr Price, who was Dr John Sappington’s son-in-law

DR. JOHN SAPPINGTON'S ANTI-FEVER PILLS.

DESCRIPTION AND TREATMENT OF INTERMITTENT, OR AGUE AND FEVER AND BILIOUS FEVER, AND ALSO DIRECTIONS FOR PREVENTING THEIR INCEPTION AND RETURN

1st.—OF INTERMITTENT, OR AGUE AND FEVER.

I consider all fevers of an intermittent character which cool off once in twenty-four hours, whether preceded by a chill or not, or whether the chill and fever rise and continue together, or if there be no chill at all. Sometimes fevers of this character continue twenty four or forty eight hours without an intermission, and sometimes it occurs every third day only. Nine tenths of the fevers of this State and most other States of this Union, partake more or less of this character, and in all their various appearances the treatment should be the same.

TREATMENT—If the patient prefers taking a purge or purge before he commences the use of this medicine, I have no objection, but it is rarely if ever necessary. A grown person will take for a dose a pill or common sized teaspoonful of the liquid* every two hours, both night and day, until the disease is broken, (always observing to shake the liquid before used,) and children will use less in proportion to age, for instance, a child eight or ten years old will take thirty or forty drops, one of three or four years old will take fifteen or twenty drops, and infants three or four weeks old will take from three to six drops, and repeat and continue as recommended for grown persons. Should the bowels be too costive, or in other words, not purge once in thirty-six or forty eight hours, give broken doses of salts, or oil, or injections, and should they purge often than twice in twenty four hours, give six or eight drops of laudanum two, three or four times a day until the looseness is restrained. Diet to be such as is suitable for a sick person, drink cold water.

2d.—BILIOUS FEVER.

This is a more obstinate and dangerous disease than Intermittent, or ague and fever, there are generally three or four days of indispotion previous to the development of fever, and generally chilly sensations for a day or two after.

When this disease is properly formed, it rarely yields to any treatment under eight or ten days, and sometimes a much longer time.

TREATMENT—In the first stage of the disease, I give a purge or one or two small doses of calomel or some other medicine that will operate upon the stomach and bowels, under any circumstances I object to giving more strong medicine, and am decidedly of opinion that a frequent repetition of them does more harm than good. After thus operating on the stomach and bowels and even without it, if the patient has become weak from the duration of disease, I commence with the pills or drops and give a dose every two or three hours, with Virginia snake root or some other sweating tea, such as hyssop, sage, or balm. Should the patient suffer much pain in the head, back, or elsewhere, give twenty or twenty-five drops of laudanum at night, children should take less, corresponding to their ages. Should the patient become debilitated from a continuation of the disease, and particularly if the hands and feet become cold, give a portion of toddy or wine every three or four hours, continuing all the time the use of the pills or drops until the disease is broken. I would prefer the bowels to be in rather a costive

than laxative condition, but should they become too inactive give oil, or broken doses of salts and injections, or if they become too loose, give six or eight drops of laudanum, two, three or four times a day, until the looseness is restrained. Diet should be light, and taken often, but in small portions at a time, drink cold water.

3d.—OF PREVENTING THE INCEPTION & RETURN OF AGUE AND BILIOUS FEVERS

The remedy I recommend for the cure of these diseases, will prevent their formation if taken in time. If used as a **PREVENTIVE**, a person should take three or four doses a day for seven or eight days in succession, then discontinue it for ten or twelve days, when it will be again used as above directed, and so on until the sickly season has passed by, persons residing in unhealthy situations, or travelling through sickly districts of country, will find the **PREVENTIVE** plan greatly to their advantage. To prevent relapses of ague and bilious fever, an individual would do well to take three or four doses of the medicine a day until his strength and complexion are restored particularly if he has had several relapses already.

The reader will find a considerable change made in these when compared with former directions, this has been produced from the fact that my **WORK ON FEVERS** is now in general circulation, and that almost every one can get a book who desires further information on these or other fevers on which it treats. Moreover, Physicians, Druggists, Apothecaries, and many other individuals, are now making and offering to the public, pills purporting to be of the same materials and quality of mine and which in many instances, no doubt, are greatly weakened as well as adulterated, and believing that in this manner frauds will be ingeniously practiced, I have caused a fac simile of my signature to be pasted around each box and these new directions will now accompany the genuine Sappington Anti Fever Pills, instead of being tied around them as heretofore.

These Pills I can recommend as being equal and similar in every respect to the pills formerly sent out by me and that persons can avoid imposition by buying **THESE** pills instead of other pills of **DOUBTFUL** strength and purity.

As the community as well as the profession are partial to acting on the stomach and bowels with some purgative medicine, and as I have admitted in my **Treatise on Fevers** that it is generally proper, and sometimes essentially necessary that some purgative medicine should be taken by the patient before he commences the use of my Anti Fever Pills, to remove any indigestible or bad accumulation from the stomach and bowels, Dr Wm Price, of Arrow Rock, Mo, my son in law, has prepared what he conceives to be a suitable purgative for that purpose, to accompany the Anti Fever Pills, and I am much inclined to the opinion that he can prepare as good a medicine of the kind as any other person—by my advice, however—to be taken as often only, and under such circumstances as is recommended in my **Treatise on Fevers**, or as is advised in the directions around my Anti Fever Pills.

*For grown persons or children, who prefer taking medicine in a liquid form, it can readily be prepared by any one in the following manner, viz pound twelve pills well, put the preparation into a vial, and add two common sized tablespoonfuls of water or whiskey to it, spirits are best, and it matters but little what kind of spirits are used. Any quantity of the liquid may be thus prepared by increasing or diminishing in a just proportion the quantity of ingredients above mentioned.

January, 1848

JOHN SAPPINGTON, Sahne Co, Mo

Price One Dollar per Box.

FIG 5 Advertisement of Sappington's pills

He probably met Sappington, but apparently they conceived no high opinion of each other. Drake learned nothing from Sappington's advocacy of the specificity of quinine. He recommends, under treatment of autumnal fever (p 782) catharsis with calomel and emesis with tartarized antimony, and bleeding. This prepared the patient "for the reception of the bark and other tonics." Quinine he regarded as a tonic only. His conception of the problem was far inferior to that of Sappington, the backwoods general practitioner, whose mind went straight through to the conception of the specific action of the drug.

A recorded experience from a physician's own lips of the classic form of treatment is that from Dr James C Finley who, in a medical periodical in 1830, told of his own experiences. By his own direction he was violently purged and had an emetic-cathartic administered. This treatment was continued for six days when "Dr Childers, a physician of great observation and experience, who very kindly attended him during the remainder of his illness considered him to be out of danger and prescribed the Sulphate of Quinine." He said his system was completely prostrated by the end of the third day. He became delirious, which was attributed to the action of the quinine and the drug was discontinued. After that he became comatose and all hope for his recovery was abandoned. When he did recover consciousness "the mind as well as the body long remained in a state of infantile weakness."

In the first chapter of his treatise, Dr Sappington gives "The author's reasons why he has departed from the practice of the old school physicians and all others in the treatment and cures of fevers." He states his disapproval of the teachings of Rush and Cullen "which was chiefly that of bleeding and acting on the stomach and bowels with emetics and cathartics as long as they thought the patient could stand them." He suggests that quinine is a tonic and not a stimulant and "is not injurious when taken in the hot stage of fevers as has been frequently said of it."

He carried this idea over into the treatment of yellow fever in which the depleting system must have been particularly exhausting, added to the natural depleting effect of the disease.

Slowly his ideas gained ground and he won converts among his professional colleagues. One physician, Dr W H Shelton, was led to throw aside the teachings of Rush and to use Sappington's pills as directed and marvelled that he was able to cure three hundred cases of fever without once resorting to the lancet.

A typical experience was that of Dr George Penn, a graduate of Jefferson Medical College, who came to Saline County in 1826, riding all the way on horseback. He formed a friendship, and afterwards a partnership, with Dr Sappington. Let me record one of his experiences as retold by Dr Thomas B Hall.

"John bringing a sack of corn with him to the mill reaches Jonesboro at 4 p m, on a crisp, clear December day. He leaves word for the doctor, who is out, to be sure to come that night to see his sister.

"Dr Penn, returning home from his rounds, already having ridden fifteen miles in his visits to the sick, receives the message and after eating his supper, prepares for the trip. All his practice is done by riding, the roads making any other means of transportation out of the question. In his stable are two horses and a mule. This latter animal being recently introduced to Missouri by the Santa Fe traders, from Spanish settlements around Santa Fe.

"This is how we acquired our famous Missouri mule, and although it is hard to believe, some were esteemed for their good riding qualities, in addition to their recognized endurance. The mule and a large white horse bear the doctor during his day travels, but by night he rides a small sure-footed sorrel, which his Negro servant now brings for him to mount. His servant properly fastens the saddle bags to the saddle. The Doctor with his pipe lighted by an ember from the hearth, places a large calibre, loaded, flint lock pistol in a holster, which he straps around his waist, mounts his horse and is off on his long trip. Crossing Salt Fork, he soon leaves the skirt of timber and is on the prairie, where the narrow trail leads through prairie grass which extends as high as his horse's head. Now and then he comes to an open place where the grass has been burnt off. Forging Blackwater, he rides from a timbered section to the prairie again and within one and one half hours from the time he has left his home, reaches the two-room log cabin of Finley, in a timbered strip near Heath Creek.

"Entering the large room of the cabin, which is lighted by a blazing fire in the large fireplace, he is greeted by Finley and his wife and the least bashful of their seven children. The room is scantily furnished, with home made furniture, in one corner is a spinning wheel, in another three long heavy flint-lock hunting rifles and a smooth bore flint-lock musket. In front of the fireplace, the two older boys are running bullets and cutting round patches from the buckskin for the rifles. The atmosphere is still full of the odors of the evening meal, cooked in the open fireplace.

"The father takes, from the mantle, a shallow open iron pan, which is filled with melted grease and has a neck out of which protrudes a wick made of tow. Lighting the wick from the hearth, he brings this crude light for the doctor to examine his daughter, aged five, who lies apathetically, covered with a buffalo robe, in a trundle bed in one corner of the room.

"An examination quickly confirms the doctor's preformed opinion of the case, for he had prescribed much quinine for the Finley family during the months of August and September and he remembered that Mrs. Finley had told him at the camp meeting on Salt Fork that it was a constant battle to force the bitter quinine down her little daughter and that she frequently became nauseated and vomited.

"A recurrence of the ague was to be expected and the child's large spleen settled the diagnosis. Drawing the hickory stool on which he is seated near the fireplace so as to have a better light and more warmth, he seats himself and places his saddle bags across his knees, one on either side, the

broad leather band connecting the bags, in this way making him a work bench across his knees. In one compartment of his bags are two, 3-ounce bottles, one containing quinine sulphate and the other calomel. He asks the father for a cupful of whiskey, which is quickly obtained from the two-gallon jug in one corner of the room. Fortunately the family has a four ounce bottle which has a cork. This is filled with the whiskey and held near the doctor, who has the bottle of quinine on the large leather band passing over his knees, thrusts a knife with a long narrow blade which he carries with him for this particular use, into the open quinine bottle. His practiced eye can tell to $\frac{1}{16}$ of a grain, the amount of quinine sulphate necessary to make two or four grains when balanced on the point of the knife. Measuring in four grain doses and counting carefully the knife eight times dumps its load in the four ounces of whiskey. This gives him a dosage of one grain to the dram and he has found it the best way to give quinine to infants and children. A few drops from a vial labeled 'Elixir of Vitrol' are added to the four ounce bottle to increase the solubility of the quinine.

"Two teaspoonfuls of this medicine are administered to the child with instructions to give thereafter, one teaspoonful every three hours night and day. When about to leave, Mr. Finley states that he has no money to pay him, but offers to pay his bill with two sacks of meal worth about 75c a sack. This the doctor assents to and instructs him to leave the meal at the mill at Jonesboro, where he already has a good many bushels to his credit for his professional services to other patients.

"Thus he expects to sell for good Spanish coin to the Santa Fe traders the next spring. Mounting his horse, he starts home by the same trail."

The amount of quinine Dr. Sappington used is an index of the thoroughness with which this countryside was de-plasmodiumed. John Farr of Philadelphia was the first chemist in America to manufacture quinine. He expressed great surprise at Dr. Sappington's orders of 500 pounds at a time. Indeed, Mr. Thomas Hart Benton tells me that it was a legend in his home that the reason Dr. Sappington first advocated quinine was that he ordered a hundred ounces and by mistake received a hundred pounds. He had a supply to be got rid of and he was a practical man. But then, as everyone knows who has seen Mr. Benton's murals, he has a somewhat mordant sense of humor.

Other diseases in this country unfamiliar to us, the successors of the pioneer physicians, were Asiatic Cholera and Typhus and "Black Leg," which was scurvy, so called on account of the petechial hemorrhages on the skin of the legs.

Dr. Sappington's drugs which he carried in his saddle bags were, besides quinine, opium in the form of powder, laudanum and paregoric, mercury, iron, oil of chenopodium, digitalis, arsenic in the form of Fowler's solution. He performed many vaccinations, carrying the lymph on bone points. He had no hypodermic syringe but allayed pain by injecting a small enema of sweet milk containing 30 to 60 drops of laudanum. He practiced counter-irritation by the free use of mustard plasters and Spanish fly ointment.

Dr Sappington's popular reputation today among those who have heard of him rather vaguely is that he was an irregular practitioner, an advertiser and almost a quack. This is partially, but not entirely, deserved. He was so passionately convinced of the truth of his cause—that the way to make the countryside healthy was to distribute quinine generally—that he felt any means justified the end. He sold his fever specific to the public. They were widely known as Sappington's Anti-Fever Pills. He excused this conduct on the grounds that there was a tremendous prejudice against quinine and if he had sold them as quinine they would not have been used, whereas he could introduce them as Anti-Fever Pills. He sold his book to the laity and wanted to get it into their hands because he realized that the profession did not accept his view perhaps they were too educated and it must be remembered that personal reminders of his existence to the extent of professional cards in the paper was the country practitioner's common practice.

It was his habit on his rounds to scatter blue grass seed over the fields by the side of the road and to try to make Missouri resemble in verdure, Kentucky.

The story of the desecration of his grave has been frequently garbled. The actual facts, however, need no retouching. He had a dread of being buried underground, and he had a lead coffin constructed, which he kept under his bed—usually filled with apples. He died in 1854 and was duly interred in the lead coffin above ground, as directed. When the Civil War came along, the Confederates ran short of ammunition and someone called attention to the magnificent supply of lead exposed at Arrow Rock. So they were ordered to take as much lead out of the doctor's coffin as they wanted and in doing so mutilated it considerably so that, as I understand, the skull was exposed for a time. William Harvey, it will be recalled, was also "lapt in lead."

This John Sappington is the sort of figure whose memory should be preserved by us. Everywhere in the United States there are materials for the record of a complete history of medical practice there. In only a few instances have they been utilized. I have been made very enthusiastic by the publication of such works as the histories of medicine in San Antonio, Texas and Sullivan County, Indiana, lately published. This is far more appropriate work for the American medical historian than delving into incunabula or Babylonian mysteries.

This is neither the time nor the place for any specific recommendations. But I hope you will not think it presumptuous of me to suggest that it is one of the legitimate functions of this College to encourage and to aid the preservation of the memories of the figures and the landmarks of our glorious past.

Note. It is a pleasure for me to acknowledge my indebtedness in the preparation of this paper to Dr Thomas B Hall of Kansas City. I have utilized not only the results of his scholarly researches into the history of Dr Sappington, but often his very words. See "John Sappington, M D" by Thomas B Hall, M D, Missouri Historical Review, January, 1930.

THE RELATION OF PULMONARY FUNCTION TO FIBROSIS AND EMPHYSEMA *

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IN a recent publication ¹ we presented a preliminary communication suggesting our ideas of intrinsic lung function. At that time we reached the following conclusions:

(1) The intrinsic function of the lungs consists in their alveolo-capillary surface-creating and self-cleansing power.

(2) Disturbance in these functions manifests itself by obliteration of some and compensatory hyperfunction of other lung areas.

(3) In pulmonary fibrosis there is a permanent loss of functioning lung units, due to failure of the intrinsic self-cleansing function, and in emphysema there occurs an irreversible loss of retraction power in the compensating lung units where the operation of the intrinsic function of creation of new breathing surface fails and the available spaces are merely overstretched by the operation of extrinsic breathing.

It is our present purpose to further elaborate and elucidate the ideas previously suggested.

THE PREVAILING CONCEPT OF LUNG FUNCTION

The prevailing ideas concerning lung function and the nature of pulmonary fibrosis and emphysema may be briefly summarized as follows. The respiratory system of air passages and pulmonary alveoli serves the purpose of ventilation. In this function the myoelastic elements of the airpassage system play the rôle of an active force in the expiratory retraction of the lung. The main activity producing ventilation is, however, the activity of the neuromuscular apparatus of breathing in the chest wall and diaphragm. The lungs act as a mere air reservoir, and the chief purpose of the lungs is to afford the breathing surface necessary for gas exchange. The structures constituting the breathing surface play a merely passive rôle. According to these ideas pulmonary gas exchange is determined essentially by cardio-circulatory function which regulates the extent of blood circulation in the lungs. Circulation and ventilation are recognized to be closely correlated to meet changing conditions, as for example from rest to exercise. It is believed that to increase gas exchange in the lungs all that is needed is to increase the work of the heart to drive more blood through the lungs.

* Received for publication June 23, 1937.

From the Tuberculosis Service, Bellevue Hospital, New York. Presented at the Clinical Session of the American College of Physicians, at St. Louis, April 22, 1937.

and to increase the work of the breathing apparatus, that is, the chest wall and diaphragm, so as to maintain adequate ventilation of the air reservoir in the lungs

According to this concept the lung, as compared with other internal organs of the body such as the kidneys, the liver, etc., has, strictly speaking, no definite function of its own. This concept was recently well expressed by Y. Henderson² as follows:

The lungs are peculiar organs in that they have little independent activity or self-regulation. Their activity is mainly determined and controlled by influences outside the lungs themselves. In their abnormal physiology the dominant influences are generally not developed in the lungs themselves, they are induced by conditions in other parts of the body.

It naturally follows that the prevailing ideas of the nature and pathogenesis of pulmonary fibrosis and emphysema are based upon the concepts of the lung and its limited function. Accordingly, pulmonary fibrosis is considered a purely structural process consisting of obliteration of the air-spaces by connective tissue the formation of which is elicited by inflammatory products or foreign matter deposits. This fibrous obliteration of the air-spaces interferes with the efficiency of the ventilatory bellows' action since it reduces the distensibility and retractility of the lung tissue. As the fibrotic process becomes more extensive, the resulting loss of reserve air-space becomes a functional handicap.

Emphysema also is looked upon as essentially a purely structural process consisting of a loss of elasticity and retractility of the tissues of the lungs of various etiology, much of which is still obscure. Here again it is held that these structural changes interfere with the efficiency of the ventilatory bellows' action and result in over expansion of the lungs because of the force of the breathing apparatus.

The prevailing, just outlined concepts about the nature and pathogenesis of pulmonary fibrosis and emphysema have been well expressed in the recent publications of McCann,³ Christie,⁴ Meakins and Christie,⁵ Kountz and Alexander.⁶

Clinical experience has, however, forced upon us the consciousness that there are many functional disturbances associated with these structural changes. Among others Knipping et al.,⁷ Richards and Cournand,⁸ have made extensive studies of these functional disturbances. However, these studies concerned themselves mainly with the disturbances of circulation and ventilation which affect gas exchange and which are considered as sequelae of the structural changes above noted. When these functions of circulation and ventilation fail, the eventual outcome is thought to be cardiac failure.

It is, therefore, obvious that in these prevailing concepts there is no suggestion that pulmonary fibrosis and emphysema might represent primary disturbances in the function of the lungs with a specific function of their

own, nor is there any suggestion that the functional failure which results from these conditions might represent organ failure of the lungs in the strict sense of that term

OUR CONCEPT OF LUNG FUNCTION

We postulate the existence of a special organ function in the lungs, analogous in every sense to the special functions of the other organs of the body. Studies of the situation existing in other organs show that the special function of each organ invariably consists in special adaptations of the structure of the units of that organ to some particular physicochemical process involved in its function. In every case the main purpose is to serve the exchange of certain substances between the blood and the specific cells of each organ. This may be either absorption into the blood of substances necessary for the life activities of these cells, or, on the other hand, the elimination of the waste products of cellular activity. The physicochemical processes involved consist chiefly of filtration of fluid and the diffusion and absorption of gases and solutes. The structure of each organ is adapted to perform its particular function.

Each organ consists of a vast number of individual units each one of which is endowed with far-reaching independence for function and also a great capacity for compensatory hyperfunction in case of failure of other units of the organ. The organ as a whole is active only in the case of an increased demand for function, and at rest only a fraction of the units are simultaneously at work. Barcroft⁹ recently described this situation for the case of the lungs as follows:

The lungs are not built for the animal as it stands or lies, they are built to subserve the needs of the animal when it is putting forth the utmost exertion of which it is capable.

Alternation of these fractions of the available organ units is the rule during rest. The structural adaptations characteristic of the organ units are linked up with the functional circulation and filtration processes, and together with the circulatory motor force behind these they form a functional mechanism which is adjusted to the pressure conditions prevailing in the circulation. This functional mechanism the motor force of which is the cardio-circulatory pump, is correlated with, and counterbalanced by, a parallel functional mechanism by virtue of which the structures of the organ units execute certain movements of adaptation under the effect of the pressures which prevail in their environment, or the effect of the tensions or active contractions inherent in their own tissues, which thus serves as another motor force behind their intrinsic functional mechanism. This is true of the kidneys, of the glands and many other organs, and we suggest that the same mechanism operates in the lungs.

STRUCTURAL AND FUNCTIONAL ORGANIZATION IN THE LUNGS

The characteristic structural units of the lungs are the air-spaces. As in the other organs we conceive that these units are endowed with far-reaching independence of action and great capacity for compensation one for another. These units function in alternation at rest, and this alternation is associated with shifts from the functional (pulmonary) to the nutritional (bronchial) circulation. The functional circulation is provided for by an exceptionally large capillary network, and there is an exceptionally abundant filtration of fluid from these capillaries into the air-spaces. We conceive that the intrinsic unit function in the lungs is served by a double motor mechanism the forces of which are acting in opposite directions, namely, the erectile force of the functional circulation which acts in a centripetal direction toward the lumen of the air-spaces, and, on the other hand, the air-space expanding force which acts in a centrifugal direction from the center of the air-spaces.

The specific physicochemical processes of gas exchange and evaporation require exposure of the circulating blood over the greatest possible surface which is constituted of a tissue membrane of extraordinary delicacy. We conceive, therefore, that it is the intrinsic function of the units of the lungs to adapt their structures so as to create such a surface, to maintain it constantly, and to regulate it under all circumstances in accordance with the requirements of the body for gas exchange and for evaporation in the lungs.

Thus, we have reached the conclusion that the creation, maintenance and regulation of internal surface adequate in quantity and quality for the momentary requirements of gas exchange and fluid elimination under all conditions is the intrinsic function of the lungs.

In our studies of this subject we have found that creation by function was implied already in Huntington's¹⁰ "selective theory" of phylogenesis of the lungs. The concept could not have been better expressed than by the statement "A man is really not winded but lunged," included in this brilliant essay. The outstanding studies of Heiss¹¹ on the embryology of the lungs have demonstrated that creation of an ever greater internal surface is the basic biologic principle of development of the lungs both before and after birth.

A Antenatal Development of the Lungs Embryologic development of the lungs takes place by biological growth of its primitive anlage consisting of an entodermal and a mesodermal component. Growth of the former results in an increase of the mass and size of the organ. As the remarkable studies of Marcus¹² have shown, growth of the mesodermal component increases the complexity of septal partitioning into new units of the organ. Wherever surface is to be greatly increased Nature resorts to such an infinite subdivisioning of available space. Antenatal lung development consisting of the centrifugal sprouting of the entodermal and the centripetal partitioning of the mesodermal component of the lung anlage, serves thus

the creation of a great number of organ units with a vast potential internal surface

B Establishment of Pulmonary Function at Birth By the recent outstanding work of Broman,¹³ Willson,¹⁴ Bremer¹⁵ our modern concepts of the functional development of the lung have become well established. This work has particularly served to confirm the concept that the first air-spaces of the lungs are produced by the mechanical disruption of the continuity of the entodermal lining of the lung units. Establishment at birth of two functional mechanisms acting in intrinsic lung function brings about the opening of the lungs' air-spaces and the creation of the breathing surface. The motor forces behind these two mechanisms are (a) centrifugal thoracic traction, as maintained by the permanent tonic activity of the neuromuscular apparatus of breathing (chest wall, diaphragm and bronchi), and (b) the centripetal erection of the pulmonary capillaries, as maintained by the pumping action of the heart. At birth these two mechanisms act together to disrupt the continuity of the entodermal covering of the lung units, to expand these into air-spaces and to expose the vast capillary surface of the lungs within the lumina of the air-spaces, which thus become separated from the outside air only by an extremely delicate membrane of the mesenchyme which is the carrier of the vascular system everywhere in the body. Disruption of the entodermal continuity is prepared for by prenatal degeneration and loosening of the lining of the terminal buds. Capillary erection is accomplished by marked increase in the pulmonary circulation as the ductus Botalli is kinked off and all blood begins to pass through the lungs. In the air-spaces thus created at birth there is established a permanent air depot (residual air) of the lungs since only a part of the air-spaces which are formed are allowed to retract at one time as function continues in alternating groups of units.

At the same time and in the same manner there is established in the lungs a permanent blood depot, that is, the large amount of blood which is rushed into the organ is transmitted to the systemic circuit only in fractions governed by the subsequent periodic rhythms of the heart and in proportion to the venous return.

It is our conception that once thus set in motion the just described functional mechanisms continue their uninterrupted course throughout life, with intrinsic lung function continuing to consist of air-space expansion and breathing surface creation by disruption of the entodermal continuity of the air-spaces and the pushing forward of the capillaries into their lumina.

C Postnatal Development by Combined Growth and Function Evidence of continued biological growth of the lungs after birth was brought forth, in addition to that already mentioned,^{13, 14, 15} by the work of Bender,¹⁶ Hilber,¹⁷ Tiemann¹⁸. With the more recent work of Bremer¹⁹ continued development of the lung throughout at least the upgrade period of life stands now conclusively proved. During the first years of life there is great

demand for additional breathing surface and air-space, which is met at first by the growth of additional new lung units. As the child grows and the intrinsic function of the lungs increases in efficiency and power, demands for increased function are being met more and more by increased function of the already available units. For a number of years, varying in each individual, there continues after birth the development of the lungs by increase of both growth and function. The principle underlying both these factors, growth and function, is internal surface enlargement by means of increased partitioning.

D Permanent Lung Function Structural Adaptation for Intrinsic Unit Function (a) *Adaptations of the membrane which serves as the breathing surface* Haldane and his associates recognized the fact that there must be some innate lung function other than that of a simple ventilatory process. They suggested that this consisted in gas secretion by the capillary endothelial membrane which separates the blood from the air-spaces. Haldane and Priestley²⁰ say

The tissue elements in which oxygen secretion occurs might either be the alveolar epithelium, the capillary endothelium, or both. It seems, on the whole, more probable that the secretory activity is localized in the endothelial cells of the capillaries since they are in direct contact with the blood.

No evidence of such secretion has ever been forthcoming. But there has been a considerable amount of new knowledge recently accumulated in the pioneer work of Landis²¹ and that of Peters²² concerning the nature of the activity of the capillary endothelial membrane in the tissues of the body in general and in the special organs in particular. We now know that it is the function of this membrane to regulate its permeability in accordance with the type of capillary filtration required for the nutrition or function of the tissue or organ in question. This is now designated as the "blood-tissue barrier" function in which the endothelial membrane of the capillaries operates in association with the mesenchyme matrix which intervenes between every cell of the body and its particular capillary. The paramount physiologic rôle played by the uninterrupted stream of tissue fluid, which maintains the mesenchyme matrix in a semifluid state, has been particularly emphasized by Schade²³ and Beneke²⁴. There is evidence that capillary permeability implies transitory changes in the consistency of the endothelial membrane.

A recent publication of Field and Drinker²⁵ contains the following statement bearing upon the semifluid consistency of the mesenchyme matrix:

It seems apparent that these passages of particles through intact capillary membranes resemble the passage of a globule of mercury through a gelatin film, a migration which leaves no trace of damage. One sees the same sort of things on passing a needle through a bit of gelatin. Again no trace remains and at all times the gelatin has retained its integrity as a membrane.

In what is perhaps the most brilliant histophysiological study yet made on the living capillary wall Clark and Clark²⁶ very recently drew the following final conclusions:

The present observations have shown that the consistency of the blood vascular endothelium is characterized by extreme lability. The rapidity with which changes in endothelial consistency may take place, and the relatively minute stimuli necessary to elicit certain of these changes, together with their reversibility, are of unquestionable physiological importance and should be taken into account in any comprehensive consideration of the morphology and physiology of blood vascular endothelium.

As the consistency of the endothelial membrane softens, fluid escapes from the capillaries. The mesenchyme matrix which transmits this fluid is also of semifluid consistency in most tissues of the body but much more so

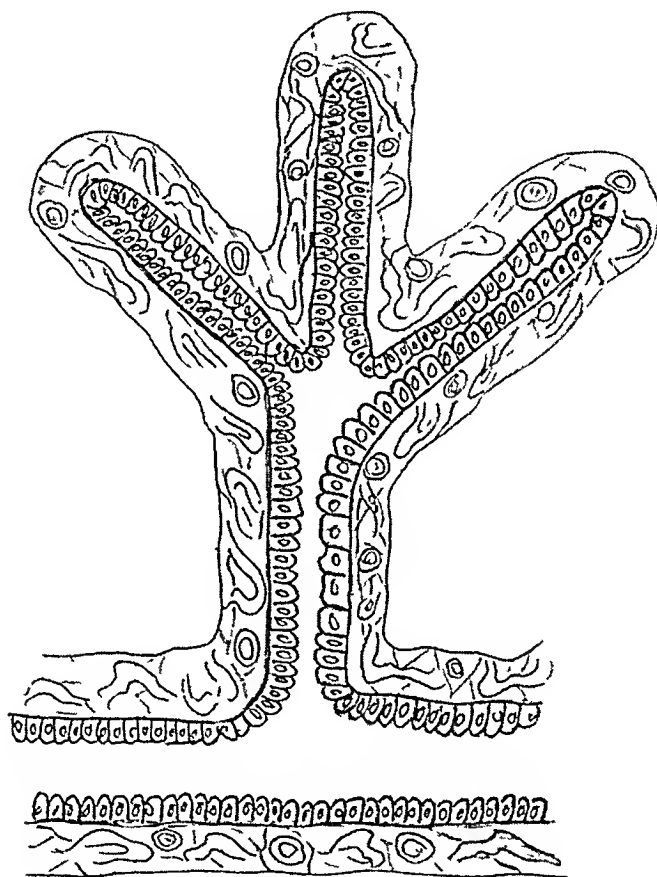


FIG 1 Prenatal unit

in some than in others. If we consider the extraordinary and constant mobility of the lungs, and the vast fluid filtration which, as shown by the studies of Terry,²⁷ Swindle,²⁸ constantly pours out from the capillaries of the air-spaces, it seems logical to assume that the consistency of the mesenchyme matrix in the lungs must be capable of unusual changes. In the lungs, gas exchange is the reverse of that in all other tissues of the body, as here oxygen diffuses into and carbon dioxide diffuses out of the blood. With this reversed gas exchange process there is closely linked a physico-

chemical process which must play a rôle in the unusual and characteristic consistency changes which make possible the histostructural changes which underlie intrinsic unit function. In our conception of intrinsic lung function we postulate definite consistency changes in the mesenchyme matrix as well as in the endothelial membrane of the lungs' capillaries as a part of the

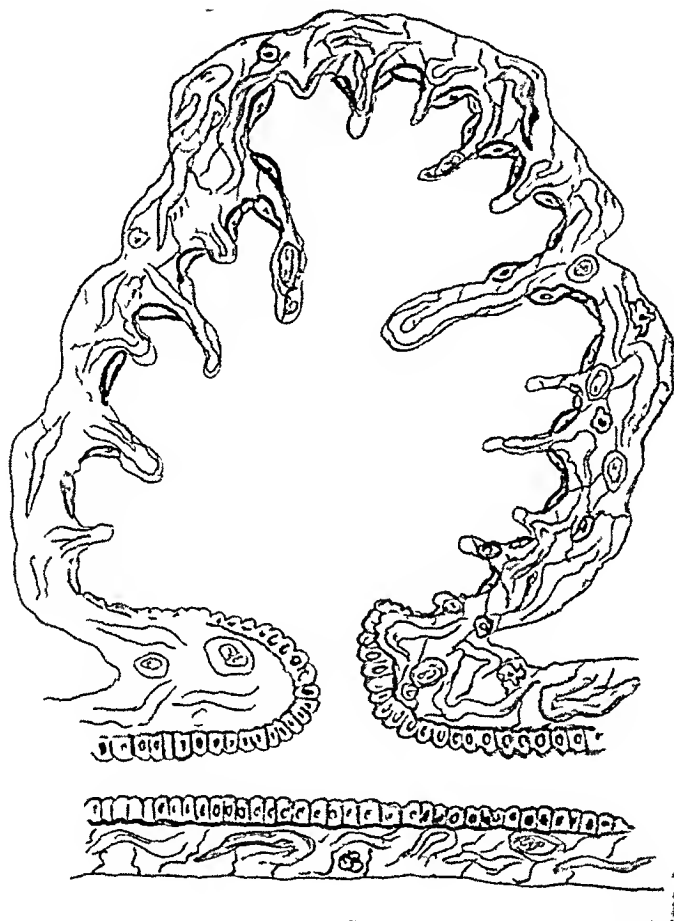


FIG 2 Unfolding and partitioning with establishment of respiration

structural adaptation of the organ to its particular function. We suggest that these changes in consistency in the endothelial membrane and in the semifluid mesenchyme matrix of the lungs are correlated with the functional mechanisms which act in intrinsic function. Thus, centrifugal thoracic traction acting upon the softened structures of the units operates as the air-space expanding force, while the centripetal erectile force in the capillaries is allowed to press forward within the softened and thinned-out mesenchyme layer. The springing-forward into the lumen of the air-spaces of these capillaries constitutes breathing surface creation.

The drawings here attached represent an attempt at schematic illustration of our concept of breathing surface creation in intrinsic unit func-

tion We are showing the lung unit in the prenatal state (figure 1), its subsequent unfolding and partitioning with establishment of respiration at birth (figure 2), and finally the alternation of resting and functioning units as indicated by the great differences in breathing surface made available by simultaneous opening as well as subdivisioning of the unit by the great number of mesenchymal partitions carrying the capillaries into the lumina of the air-spaces (figure 3)

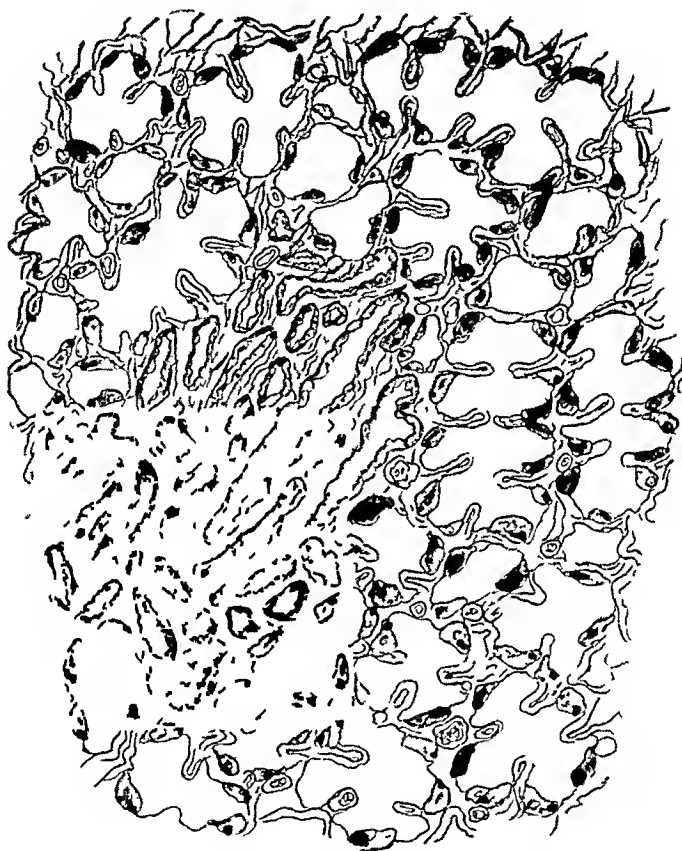


FIG 3 Alternating resting and functioning units

(b) *Adaptation of the other structures of the units* In animals with low gas exchange requirements (amphibia) the air-spaces of the lungs are completely lined with epithelium and the lungs are perfused only periodically, the circulation in the organ as a whole being short-circuited from the right ventricle to the aorta, just as it is in the human fetus. In animals with higher gas exchange requirements (birds) the lungs consist of one large air-sac with a separate air inlet for fresh air and an outlet for used air, one capillary network being placed in the center of the air-sac, there is no tissue layer between the capillary surface and the air in the sac, the breathing surface being altogether naked.

Man stands between these two extremes as far as gas exchange requirements are concerned. Accordingly, the internal surface of the human lung is naked only in part, and while the organ as a whole cannot be shunted from the circulation, partial shunting is possible within the individual units. This we construe to be a structural adaptation for increased unit function. For years anatomists have debated the question as to whether the air-spaces of the human lung are lined or naked. The answer from our hypothesis would be that it is lined at some times and naked at others, depending upon the alternating periods of rest and active function. Resting units are fully lined, their walls are thickened and they have the retracted appearance of what Seemann²⁹ has designated as "physiological atelectasis." The recent and particularly exact studies of Verzar³⁰ have given us conclusive proof of the truly physiologic nature and prevalence of such atelectatic areas in the lungs normally. The functioning units are expanded, their walls thinned out, their epithelial lining discontinuous, with the cells few and far between, leaving naked stretches where the capillary surface is exposed, with only an extremely thin mesenchyme membrane separating it from the air-spaces, as was so well demonstrated recently again by Clara.³¹

In the resting units the circulation is for nutrition the blood supply of which Daly³² has recently again shown to be coming from the bronchial arteries by anastomoses with the capillary net of the air-spaces derived from the pulmonary artery. That these capillaries are thus perfused alternately by the nutritional circulation from the bronchial artery and a functional circulation from the pulmonary artery has been claimed already by Havlicek.³³ Perfusion for nutrition demands the intervention of a mesenchyme matrix different in quantity and in quality from that required for functional circulation. The original mesenchymal conditions prevail in the resting units which are being perfused only for nutrition, while in the functioning units the mesenchymal layer is softened and thinned out into a membrane of extreme delicacy adapted to functional circulation and filtration, and this constitutes the breathing surface in the functioning lung units.

The tidal volumes of blood are distributed between the functioning units by means of the functional capillary bed. Some blood is always held in the resting units as a blood depot which varies in proportion to the number of resting units. The existence in the lungs of such a blood depot was first assumed by Rappaport³⁴ and has been fairly substantiated by the recent work of Hochrein,³⁵ Pfeiffer,³⁶ Sjostrand.³⁷ Some blood passes the lungs by way of these depot channels which thus serve as shunting channels of the pulmonary circulation. Being shunted from the breathing surface of the lung units, the perfusion in these channels is greater as the requirements for gas exchange are less, as for example in sleep, and, on the other hand, is markedly diminished when the gas exchange requirements are increased, as in exercise, and a large proportion of the lung units are in active function. This accounts for the high oxygen tension difference between the alveolar

air and arterial blood at rest, and its disappearance during exercise, as found by Bock et al³⁸

We conceive of increased capillarization to be the key to increased unit function in the lungs, just as it is in some other organs such as the kidney. Increased capillarization and increased capillary filtration result in the consistency changes in the endothelial membrane and the mesenchyme matrix above described, resulting in greater efficiency in the functional mechanism, and are a part of increased intrinsic lung function.

(c) *Self-Cleansing* Intrinsic unit function requires the most intimate exposure of as extensive and delicate a breathing surface as the momentary gas exchange requirements demand. This intimate exposure is present only for short periods and in a fraction of the units. But, when it occurs, the air-spaces are flooded by an abundant fluid stream which drains out into the lymphatics and air-passages, not only the fluid but also dissolved material and desquamated cells in the lumina of the air-spaces, laden with digested foreign matter. The self-cleansing rôle of the fluid stream was already appreciated by Irwin³⁹. Intrinsic unit function automatically affords a self-cleansing of the air-spaces and of the breathing surface, so that we consider self-cleansing as a component of intrinsic unit function. The efficiency of self-cleansing depends upon the efficiency of the intrinsic function as a whole and fails when that function is disturbed.

E Lung Function (Intrinsic Unit Function) and Ventilation (Extrinsic Breathing) These are two altogether separate functions which are intimately correlated. The neuromuscular apparatus of breathing acts in both, but the distinction between intrinsic function and extrinsic breathing is very definite inasmuch as the former depends upon the permanent tonus, while the latter is accomplished by the periodic contractions and relaxations of the neuromuscular apparatus. This concept rests on the outstanding work of Hess⁴⁰ which established the fact that the neuromuscular apparatus of breathing (in the diaphragm, chest wall and bronchi) functions by maintenance of neuromuscular tonus, that the permanent state of inflation of the lungs is maintained by the permanent tonic component, and that the superimposed pulmonary excursions are accomplished by the shifts in neuromuscular tonus manifesting themselves in the periodic increased contractions and partial relaxations of the neuromuscular apparatus. Demonstration of the exact rôle of the "self-controlling," i.e., "proprioceptive" reflexes in the regulation of both the permanent tone as well as the periodic contraction of the neuromuscular apparatus of breathing was the contribution of Fleisch⁴¹.

Like capillary perfusion, intrinsic unit function is uninterrupted but operates in alternating groups of units. It depends on the constant negative pressure, that is, the permanent thoracic traction, which is maintained by the basic tonus of the neuromuscular apparatus of breathing.

Like cardio-circulatory function, ventilation, that is, the movements of

the lungs, is periodic, depending upon the rhythmic contractions and relaxations of the neuromuscular apparatus of breathing

Intrinsic unit function, however, is regulated in accordance with the momentary requirements of the tissues of the body and, like similar functions in other organs, is controlled by regulation simultaneously through chemical hormonal and vegetative nervous stimuli. The neuromuscular apparatus of breathing which acts both in intrinsic lung function and in ventilation is under the combined control of the vegetative and the voluntary (cerebrospinal) nervous system. For the transmission of stimuli from the vegetative to the voluntary sphere, which is necessary for this combined control, Nature has provided the proprioceptive reflex regulation, so called by Hoffmann⁴² who discovered these reflexes and revealed their significance. The permanent tonic activity of the neuromuscular apparatus of breathing which is active in intrinsic lung function is brought under vegetative nervous control by these proprioceptive reflexes. The manner in which the vegetative (regulatory) nervous system controls the tone and automatic contractions of the breathing musculature by way of the proprioceptive fibers traveling in the pulmonary vagus, has recently been discussed by Nakanishi⁴³ in a particularly illuminating fashion. The periodic ventilatory activity of the apparatus of extrinsic breathing, while chiefly under voluntary control, is also subservient to intrinsic lung function which is under vegetative nervous control.

Ventilation is thus always adapted to the momentary level of intrinsic lung function. With the demand for increased lung function, as in exercise, there takes place an increase in the intrinsic unit function and also in the number of functioning units, and with this ventilation must also increase proportionately. We conceive that there is considerable variation between individuals in their capacity for the adaptation of intrinsic function. Some individuals can meet the requirements for gas exchange by fewer units functioning with greater efficiency, while in other individuals the same demand must be met by calling upon the simultaneous function of a greater number of units. In the latter case quantity has to make up for quality, the air turnover must be proportionately greater and, consequently, the ventilation must be relatively increased. Thus it is seen that ventilation may compensate for intrinsic lung function to a considerable extent.

On the other hand, within the limitations of his capacity an individual may compensate for deficient ventilation by increased intrinsic function. We conceive that the true capacity for pulmonary function as a whole is the efficiency of the intrinsic lung function factor. Excessive ventilation is more often a sign of low pulmonary capacity, while low ventilation is more apt to be associated with an intrinsic lung function which is compensatorily increased rather than deficient. Direct support for this contention may be found among others in the work of Herbst,⁴⁴ but particularly in the more recent study of Thomas⁴⁵ in which he concluded that

It is important to realize that increase in residual air may constitute one factor in a method of increasing oxygenation of the blood and should not be accepted per se as evidence of reduced pulmonary efficiency

F Respiro-Circulatory Correlation That there is a definite correlation between the circulatory and respiratory functions is well recognized, although not by any means completely understood. For our purposes we wish to sharply distinguish the correlation which exists in general between ventilation and circulation, and that correlation which we assume to exist between intrinsic lung function and the pulmonary circulation proper. The ventilatory excursions of the chest promote the venous return to the right heart in one phase, and the action of the left heart in the other. This represents the correlation between ventilation and cardiocirculatory function in general. In our conception of intrinsic lung function the degree of functional capillarization in the lung is of fundamental importance, as are certain phenomena in the pulmonary circulation such as the blood depot function and shunting as above explained. Just as extrinsic breathing and intrinsic lung function are correlated with each other, so we conceive that the cardio-circulatory function of the body as a whole is coordinated with ventilation so as to adapt the changes in the pulmonary circulation to the demand of increased lung function.

FIBROSIS AND EMPHYSEMA AS INTRINSIC LUNG FAILURE

It is obvious that these concepts of intrinsic lung function must materially affect our ideas concerning the pathogenesis of fibrosis and emphysema. We have already indicated that one of the essential features of intrinsic lung function is the self-cleansing mechanism by which the air-spaces are kept clear and the breathing surface clean, by the constant and rapid elimination from the tissues of the lungs of everything which interferes with the forces operating in air-space expansion and breathing surface creation. This includes the elimination of large quantities of fluid, the disposal of many waste products reaching the lungs from the blood, and the disposition of extraneous matter reaching the lungs by inhalation and also through the desquamation of cellular material. We suggest that interference with the normal fluctuations in the consistency of the capillary endothelial membrane and also of the mesenchyme matrix, tends to bring about an increase in density and a hardening of the consistency of the mesenchyme. This materially affects its characteristic permeability and its mobility and thus interferes with its adaptations required in the operation of intrinsic unit function. This hardening and decrease of mobility also interferes with the self-cleansing function and thus leads to fibrosis with obliteration of the units affected. These changes may result from the inhalation of foreign matter, as in silicosis, or they may be the effect of inflammatory processes of various kinds, or they may be due to irritating toxic substances coming in from the blood, or they may be due to abnormal circulatory changes associated with disease.

of the heart or the kidney Fibrosis and obliteration of the affected units are the result

For whatever reason various lung units may thus be excluded from intrinsic function they still remain subject to the ceaseless air-space expanding force of thoracic traction Wherever capillary filtration and the associated alternations in the consistency of the mesenchyme matrix have ceased, the degree to which any individual lung unit may resist or must yield to expansion will depend upon the intensity of the thoracic traction force on the one hand, and upon the extent and rate of the increase and hardening of the mesenchyme on the other

Increase and hardening of the mesenchyme matrix obliterating the air-spaces constitutes fibrosis

Expansion of the unit without simultaneous breathing surface creation constitutes emphysema

These two processes go hand in hand and are, therefore, practically always to be found in combination Sometimes fibrosis will prevail over emphysema, while at other times the emphysema prevails over the fibrosis It thus lies in the very nature of intrinsic lung function coordinated with the mechanical forces in operation, that a unit permanently excluded from function must either become transformed into a fibrotic band or nodule which may either yield or resist to breathing, or it must be expanded into an ever greater air-space the elements of which are being gradually stretched out of existence When both of these processes occur in a conspicuously large number of units we speak of pulmonary fibrosis and emphysema which thus represent a manifestation of chronic failure of intrinsic lung function

Clinically the term emphysema is applied to permanent distention of the lungs to a degree which normally prevails transitorily in the increased function which occurs during exercise^{4, 5} Associated with this is a permanent increase in the residual air content of the lungs, which in turn implies a proportionate restriction of their vital capacity As in exercise so in emphysema expansion of the lungs beyond the rest volume takes place in response to a demand for increased intrinsic lung function, which is responded to by the simultaneous function of a greater number of units rather than a greater efficiency of the intrinsic function of the individual units Just as in exercise so in emphysema there is an individual limit to the possible expansion of the organ and to the feasible number of simultaneously functioning units compatible with the requisite degree of ventilation Ventilation must always increase proportionately with the increase of simultaneously functioning units The permanent state of expansion and the periodic excursions of the lungs both represent the activity of the neuromuscular apparatus of breathing The state of expansion depends upon the state of the basic tonus, and the periodic excursions upon the rhythmic contractions of this apparatus^{40 41} This is a reciprocal arrangement so that one can increase

only at the cost of the other if the basic tonus must increase to hold the lungs in greater permanent expansion, then the periodic contractions must diminish in amplitude, that is, ventilation must suffer in efficiency. Hence, if the number of functioning units must be increased beyond a certain limit this can take place only at the cost of ventilation.

Increase in the number of simultaneously functioning units represents a type of compensatory increase in intrinsic lung function, which results in better utilization of the lung air, i.e., relatively increased oxygen absorption. This has its limitations beyond which improvement in intrinsic function must be bought at the cost of decreased ventilation, i.e., carbon dioxide retention. This type of compensatory increase in intrinsic lung function takes place also when the interference is primarily with ventilation for some reason, as in obstruction to movements of the chest such as chest deformities, conditions immobilizing the diaphragm, or those interfering with bronchial function as in asthma and bronchial obstruction, etc.

With progressive obliteration of an increasing number of lung units more of the available units are called upon for replacement, so that the number of simultaneously functioning units increases as a matter of compensatorily increased lung function. This necessarily implies a corresponding increase in the permanent expansion of the lungs, and when this goes beyond the limit compatible with the requisite degree of ventilation we have emphysema associated with restriction of vital capacity.

This emphysema, however, is still compensatory in nature, although it may persist throughout life. But, in the final analysis it is only functional not structural in nature, and should the patient die during this phase little evidence of this emphysema will be manifest in the structures of the organ. This explains the great discrepancy between the clinical and the pathologic findings of emphysema.

When fibrous obliteration of the units reaches such proportions that the requisite number of units for compensatory function are no longer available, the force of thoracic traction acts to keep the still available units in constant expansion and tends to gradually overexpand them, so that the air-spaces become dilated and thinned out and may reach the stage of bullae so characteristic of advanced emphysema. These bullae represent air-spaces formed by the coalescence of lung units in which intrinsic function, particularly breathing surface creation action, has ceased. Emphysema thus represents air-space production without corresponding breathing surface creation.

We may conclude, then, that just as pulmonary fibrosis may in the final analysis be interpreted as failure of self-cleansing, so emphysema in the final analysis may be explained as failure of breathing surface creation.

Fibrosis and emphysema thus represent a form of organic asthenia of the structures which function in breathing surface creation and in self-cleansing. This asthenia manifests itself by the insufficiency of the erectile

force of the capillary blood flow and the drying-up of the stream of tissue fluid which normally pours into the air-spaces. Accompanying this there are functional changes in the quantity and quality of the mesenchyme matrix which plays the paramount rôle in both breathing surface creation and in self-cleansing. The result is an ever decreasing partitioning of the air-spaces, that is, loss of internal breathing surface, and increasing coalescence of the air-spaces, with no evidence of where the tissue elements have disappeared. The structures in which the reservoir of the function-bearing mesenchyme has become exhausted disappear in the self-cleansing process which acts ceaselessly in coordination with the uninterrupted air-space expanding force. Whole units and groups of units are thus cleansed out and ever larger bullae are thus produced.

This organic asthenia may represent a congenital weakness of the organ, or the result of damages and injuries produced by a great variety of pathological processes occurring during the life of the individual, and, finally, it may be the result of the natural involution process of old age.

All of these factors are naturally subject to many variations in the same individual and particularly between different individuals. Thus, the great differences in individual predisposition to fibrosis and emphysema in the younger age group are explained, as well as the variations in the period at which they develop among the more aged.

PULMONARY FAILURE AND DECOMPENSATION

We have thus indicated that according to our conceptions pulmonary fibrosis and emphysema represent a chronic decompensation of the function of the lungs. Clinically this is regularly manifested by the decompensation syndrome the most outstanding symptom of which is dyspnea.

As fibrosis and emphysema become more advanced we observe clinically episodes of more acute pulmonary decompensation. These take the form of more acute dyspnea, cyanosis, with evidence of pulmonary edema. These attacks may vary in intensity and duration and will often clear up temporarily. Finally, however, all cases arrive at the stage of acute pulmonary edema which has usually been interpreted to mean cardiac failure. According to our observations, however, it is not the heart which fails but rather it is its continuing compensatory effort which intensifies the pulmonary embarrassment. For, the more lung units are out of function the more the circulation must increase in the remaining available units. But, with such a vast proportion of the lungs' units failing to perform their function, the blood continuing to come into the lungs only increases the burden upon the decreasing number of still functioning units, and so these too become unable to arterialize and transmit the blood. We then observe complete failure of the lungs, manifesting itself in pulmonary edema. The self-cleansing function and the breathing surface creation having already been taxed to their full limit, also fail entirely, and the patient dies of acute pulmonary decompensation or failure.

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AN ARTICLE CONTRIBUTED TO AN ANNIVERSARY VOLUME IN HONOR
OF DOCTOR JOSEPH HERSEY PRATT

THE DIFFERENT CLINICAL GROUPS OF XANTHOM- ATOUS DISEASES, A CLINICAL PHYSIO- LOGICAL STUDY OF 22 CASES *

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* Received for publication August 17, 1937

From the Medical Clinic of the Boston Dispensary and Tufts College Medical School,
Boston

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INTRODUCTION

THE group of lipid diseases comprising xanthomatosis, Gaucher's disease and Niemann-Pick's disease has been considered in the newer literature, following the idea of L. Pick,^{85, 86, 87} as a disturbance of the lipid metabolism of the whole organism. In essential xanthomatosis, cholesterol and cholesterol esters, in Gaucher's disease cerebroside, and in Niemann-Pick's disease sphingomyelins are involved.

This paper deals with essential xanthomatosis only, on the basis of observation of different clinical groups of this disease. We have set as our task the elucidation of the pathogenesis of this disease and to investigate whether the basic disturbance is in the intermediary cholesterol metabolism or whether it lies in the xanthoma cell (foam cell) itself, the characteristic feature of the xanthomata.

To approach this problem it is necessary to discuss in detail our present knowledge of the normal metabolism of cholesterol, and to consider whether the facts warrant the general assumption that xanthomatosis is due to a disturbance of the cholesterol metabolism in the whole organism.

THE METABOLISM AND FUNCTION OF CHOLESTEROL

Whether the body is able to synthesize and to disintegrate the sterol-skeleton is a fundamental question. The possibility of a synthesis of the sterols has been investigated from different points of view. Gamble and Blackfan,⁴² carrying out balance experiments with infants on a milk diet, believed that cholesterol was formed in the body as shown by a greater output than intake. My coworkers and I¹²⁸ showed similar results in balance experiments on adults (if the present knowledge based on the work of Schonheimer,¹¹⁶ that plant-sterols are not absorbed, is applied to the figures of our experiments). At the same time Schaber and I¹²⁹ were able to substantiate the fact that the total amount of sterols increases in eggs during incubation. Today the synthesis of sterols in the organism is demonstrated beyond doubt in many experiments. I may mention the experiments of Schonheimer¹¹⁰ on laying hens, and also the studies of Jenke and myself¹³³ on dogs with bile-fistulas, which establish the fact that 2 gm. of bile acids are produced daily from dogs independent of the sterol content of the food.

It is not definitely known in which organs and cells the sterol-synthesis is accomplished. Cholesterol-determinations in cases of yellow atrophy of the liver¹³¹ and experiments on hepatectomized dogs,¹³² however, point to the liver. In both of these conditions we found a decided drop of total cholesterol in the serum.

The mechanism of the formation of the sterol-skeleton in the body,

however, is entirely unknown. It is not even possible to determine whether cholesterol and bile-acids are formed from proteins, carbohydrates or fats in the animal organism. Studies relating to this question by my coworkers Jenke^{130, 134, 56} and Schindel^{105, 106} on dogs with bile-fistulas produced no clear results. Only experiments on lower plants hint at the material from which the sterols in plants may be synthesized. According to Massengale, Bills and Prickert,⁷³ the amount of ergosterol formed by *Saccharomyces cerevisiae* depends on the amount of sugar present, and sugar is the only organic foodstuff in the basal medium supplied in these experiments. Polysaccharides occasioned the formation of greater amounts of ergosterol than did the monosaccharides. It is noteworthy that the presence of sulphite decreases the sterol production of yeast in such a solution (McLean and Hoffert⁶⁹).

The destruction of the ring system of cholesterol in the metabolism has not yet been proved. Patients suffering from nodular xanthomatosis with a very large amount of cholesterol in the blood exhibit a considerable loss of cholesterol when kept for a long period on a cholesterol-free diet. In two balance experiments about 20 gm of cholesterol disappeared within seven weeks without being recovered in the stools. The output of sterols in the period mentioned was low (Schonheimer,¹¹⁵ Schilling¹⁰⁴). Analyzing the whole bodies and excreta of rabbits, cats and mice after feeding cholesterol-rich diets, Menschnik and Page,⁷⁴ Schonheimer and Breusch¹¹² recovered only a part of the amount of cholesterol given. These experiments, however, indicate merely that cholesterol, fed and retained, cannot be found again with digitonin precipitation. A recent paper by Bertha Ottenstein⁸² clears up this supposed disappearance of cholesterol in the body, by showing a disintegration of the sterol-skeleton due to the action of bacteria in the intestine. She demonstrates further that colon bacilli from the large intestines are particularly active in this respect. Thus a deficit of cholesterol in balance-experiments may be due to bacterial destruction and not to disintegration of the sterol-ring system in intermediary metabolism. A gap in the sterol-skeleton produced only by irradiation of ergosterol with the formation of vitamin D is no proof of metabolic disintegration. As long as derivatives of sterols, indicating a decomposition of the sterol-skeleton, are not discovered, the destruction of the sterols in the intermediary metabolism is not conclusive. Summing up, it may be said that the synthesis of the sterol-skeleton in animals is evident but the destruction of the sterol-molecule in the metabolism is not proved.

The changes which the body is enabled to make in cholesterol are significant but few. By means of an esterase the alcoholic hydroxyl is esterified with different fatty acids. The esterification of cholesterol produces a change in its physical properties important for its absorption and transportation in the organ fluids as well as for the composition of the cell-lipoids. Although an esterase is present throughout the body, the liver plays an

important rôle in determining the ratio of cholesterol to cholesterol esters Schaber and I¹³¹ showed that the esters are diminished in the serum in cases of parenchymatous liver disease, a fact confirmed by many investigators

Schonheimer¹¹¹ substantiated the presence of dihydrocholesterol in the serum and in tissues in normal humans, later on demonstrating an increase of dihydrocholesterol in a patient with nodular xanthomatosis¹¹⁵ These experiments (Schonheimer and Hrdina¹¹⁶) gave evidence that dihydrocholesterol in the tissue indicates a reduction-process in the body Genuine reduction-processes are not known in the intermediary metabolism There are combined processes of hydrogenation and dehydrogenation coupled with an oxygen-acceptor It may be that the dihydrocholesterol in the tissue originates from such a process In contrast to dihydrocholesterol the isomeric coprosterol does not occur in the tissue or in the intermediary metabolism Allocholesterol, which is supposed to be the unsaturated stereo-isomeric sterol of coprosterol, is not discovered in the body according to Schonheimer¹¹⁴ Thus coprosterol must originate from cholesterol in the intestines In the formation of coprosterol from cholesterol a change in the steric configuration must be accomplished on carbon-atom 5 This steric transformation is supposed to be produced by activity of bacteria In a recent paper Schonheimer,¹¹⁷ by means of an ingenious method of adding deuterium instead of hydrogen to the double bond, indicated the probability of a mechanism of the steric transformation of cholesterol to coprosterol First, the stero-isomeric cholestenone is formed from cholesterol by oxidation and then undergoes reduction to coprostenone and coprosterol The possibility of a steric transformation of cholesterol in the body is of importance because the bile acids are members of the coprosterol-series Although coprosterol and allocholesterol have not yet been recovered in the intermediary metabolism it was thought to be possible that the bile acids originate from sterols of the coprosterol-series Indeed in our^{130, 134} experiments on dogs with bile-fistulas the injection of allocholesterol and coprosterol increased the output of bile acids However, in dogs the amount of bile-acids produced daily was found to be so great, namely, about 2 gm, that the bile-acid formation must originate from a biological synthesis of the sterol-skeleton in the liver and not from a metabolic transformation of sterols already existing in the body The results of our experiments were confirmed by Schonheimer¹¹⁸ and his coworkers by adding deuterium on the double bond of cholesterol and feeding this deuterium containing cholesterol to animals The bile acids produced afterwards in the organism did not contain deuterium Thus we may assume that cholesterol absorbed or synthesized in the metabolic processes is excreted as unchanged cholesterol in the bile and in the intestines There cholesterol is transformed for the most part into coprosterol and probably undergoes a bacterial destruction to an unknown extent The ability of bacteria to destroy organic ring compounds is one of the most important facts in the equilibrium of the organic

world. Thus the uni-cellular organism prevents the preponderance of cyclic organic compounds, which are synthesized by higher plants and animals, over aliphatic substances in nature. The presence of certain bacteria in the bowels therefore is wisely provided for in all animals.

The ability of the intestine to excrete cholesterol is not the same in all animals. The herbivorous animals cannot excrete cholesterol in noticeable amounts although they are able to absorb animal cholesterol experimentally added to their plant food. Therefore, atheromatosis might be produced experimentally by feeding cholesterol to herbivorous animals. The question arises, which kind of sterols is absorbed in animal and human bodies? The experiments of Schonheimer¹¹⁶ and his coworkers demonstrate that neither herbivorous nor carnivorous animals absorb plant sterols. Only small amounts of ergosterol are absorbed. It is a noticeable fact that dihydrocholesterol, although it is formed in the intermediary metabolism and excreted in the intestines, is not reabsorbed. Cholesterol is the only animal sterol which undergoes absorption from the intestines. It is excreted in the bowels and reabsorbed to a large extent.

This marvelous selective absorption of sterols, unexplained in its mechanism, is of great importance for the sterol metabolism, protecting the body against an accumulation of sterols. The fact that cholesterol is synthesized in the metabolism prevents a deficiency of cholesterol in the organism due to an unsatisfactory absorption. In regard to the excretion, however, diseases may originate from an accumulation of cholesterol due to an unsatisfactory discharge.* This matter of clinical interest will be discussed later on.

The function of cholesterol itself in the metabolism is rather doubtful, although its wide occurrence in the animal kingdom is supposed to give a hint of its necessity. The main function of cholesterol is indicated in the fact that cholesterol and cholesterol esters are present in a constant percentage in every lipid mixture occurring on the surface or within the cell. Cholesterol is a hydrophobic colloid while the monoaminophosphatides like lecithin are hydrophylic colloids. The diaminophosphatides occupy a middle position between the two so far as their behavior towards water is concerned. The correct mixture of the lipoids in the cells depends on the presence of an adequate amount of cholesterol. Thus one of the important functions of cholesterol is seen to result from its physical properties, especially in regard to the equilibrium of the lipid mixture, which controls the exchange of fluid as well as the exchange of fat-soluble material in the cell.

Some authors attach significance to the fact that cholesterol neutralizes hemolytic substances, for example saponins, different glycosides, and animal venoms. To accomplish this the double bond and the hydroxyl group in the sterol molecule must be available. Esters and saturated sterols exhibit

* Bareda¹¹ proved that a clinical tolerance test by feeding cholesterol in oil and examining the serum cholesterol after a certain time gives unsatisfactory and not uniform results because the test depends on too many uncontrollable factors.

no anti-hemolytic efficiency. In a similar way cholesterol is supposed to be effective against some of the bacterial toxins. This conception is based on its action in vitro against tetanus toxin. Furthermore, it is observed that in most febrile infectious diseases blood cholesterol is reduced at the climax and also in the terminal stages of infectious diseases. It may be admitted, that while cholesterol forms insoluble addition products with anti-hemolytic substances, like tetanus toxin, in vitro, most of these substances, or reactions occur neither in normal nor in the diseased body. The claim then, that the main function of cholesterol must be a detoxifying one is not satisfactorily proved.

Hypotheses referring to the function of cholesterol are as numerous as they are fragile, so that the mention of a new hypothesis may be presumptive. The presence, however, of dihydrocholesterol in the tissues, as discovered by Schonheimer¹¹¹ can be explained by the assumption that there is an oxidation-reduction system in the body within which cholesterol-dihydrocholesterol plays the same rôle as succinic and fumaric acid do in an already known system of this kind.

The cells in the body break down and are rebuilt. In this process cholesterol becomes available and is needed. In addition to its metabolic utilization cholesterol is synthesized, excreted and accompanies neutral fat wherever fat is transported in the body. The concentration of cholesterol in the blood, therefore, depends on these different occurrences, so that an increase or decrease of cholesterol and cholesterol esters in the blood is not due to a one uniform cause.

Hypercholesteremia, whether due to cholesterol esters or to free cholesterol, is a symptom which indicates that the excretion of cholesterol does not keep pace with the endogenous and exogenous supply. Simultaneously with the symptom of hypercholesteremia, cells appear in different organs filled with lipids which are mainly sterols. These cells, which are called foam-cells, according to their appearance, or xanthoma cells according to their content, may after some time give up their cholesterol to the blood. There remains a granulomatous scar tissue consisting of giant cells, lymphocytes, and connective tissue. Before we enter into the discussion of the mechanism of the xanthoma formation, different clinical pictures of the xanthomatous diseases will be presented.

XANTHOMATA OF TENDONS AND TENDON SHEATHS

Case 1 R. S., a 65-year-old Jewish widow, noticed first the appearance of "burning lumps" on the knuckles of the third finger of each hand at the age of 35. When 55 years of age, similar lumps developed above both heels, and at the age of 62 a small node appeared on the right elbow.

She stated that a tumor of the uterus and both ovaries had been removed when she was 42 years old. She had gained much weight after the operation. She had been married three times, and had no children.

One brother had small but similar lesions on his fingers.

She was an elderly obese woman of the matron-type, not icteric. She had no



FIG 1 Case 1 Xanthomatous nodules of the tendon and tendon sheaths of the hand



FIG 2 Case 1 Xanthomatous nodules on both Achilles tendons

xanthelasma Liver and spleen were not palpable In the extensor tendons of both third fingers were circumscribed xanthomata measuring about 3 by 6 cm movable only with movement of the tendon in the region of the phalangometacarpal joint There was another small node on the fifth finger of the left hand and large xanthomata in the region of both Achilles tendons

Changes in the right knee joint, clinically and roentgenologically were characteristic of osteoarthritis, but no cystic bone lesions were present The patient was admitted to the hospital on 10/21/35

The following table gives the cholesterol findings in the blood serum

	Serum Total Cholesterol	Free Cholesterol	Cholesterol Esters
10/22/35	360 mg %	200 mg %	160 mg %
10/29/35	368	240	128
11/7/35	347	191	156
11/19/35	351	187	164
11/26/35	345	148	197
12/2/35	338	158	180
12/17/35	420	200	220
1/15/36	388	198	190
4/17/36	394		
6/2/36	440	124	316
7/9/36	423	163	260
9/10/36	390	70	320
11/13/36	364	113	251
2/20/37	284	100	184

A cholesterol-free diet was begun on 10/22/35 and continued until discharge on 11/29/35 Thyroid extract was administered as follows from 11/20/35, gr 1, b i d , from 11/20 to 11/29/35 gr II, t i d The thyroid was discontinued on 11/29/35

A small subcutaneous nodule appeared below the right knee cap during the diet treatment A biopsy from the node in the tendon of the third right finger showed the xanthoma to be intimately connected with and situated between the fibers of the tendon The section was composed of dense interlacing cellular strands and bands of collagenous tissue interspersed by innumerable varying sized groups of large foam cells Among these swollen xanthoma cells were occasional binucleated cells and rare mitotic figures There were no large giant cells

A smear from the first specimen showed many cholesterol crystals Analysis of dry tissue total cholesterol 9 mg per cent, total phospholipids 11 mg per cent

There was no recognizable change in the size of the lesions of the tendons during the period of cholesterol-free diet, which, however, the patient did not follow strictly Small xanthelasma-like yellow lesions in the skin of the nose at the site of the pressure of her eye-glasses appeared in December 1936

Case 2 R S, a 55 year old salesman, brother of Case 1, had noticed nodes on his knuckles for several years He had never been seriously ill and had no complaints

He showed a small xanthoma on the extensor tendon of his right fourth finger at the first interphalangeal joint He also showed circumscribed swellings of both Achilles tendons, 4 by $\frac{1}{2}$ cm The liver and spleen were not palpable

Serum total cholesterol	210 mg per cent
" free cholesterol	107 " " "
" cholesterol esters	103 " " "

Discussion In 1879, Calcott Fox³⁹ in England and Carry²⁷ in France first described patients suffering from xanthomata of the tendon sheaths

The patient described was a member of a family which had suffered from so-called "gout" for three generations. The diagnosis of "gout" was previously made in the girl described, although at the age of seven she had yellowish xanthomata plana in addition to the tendon sheath nodules. The

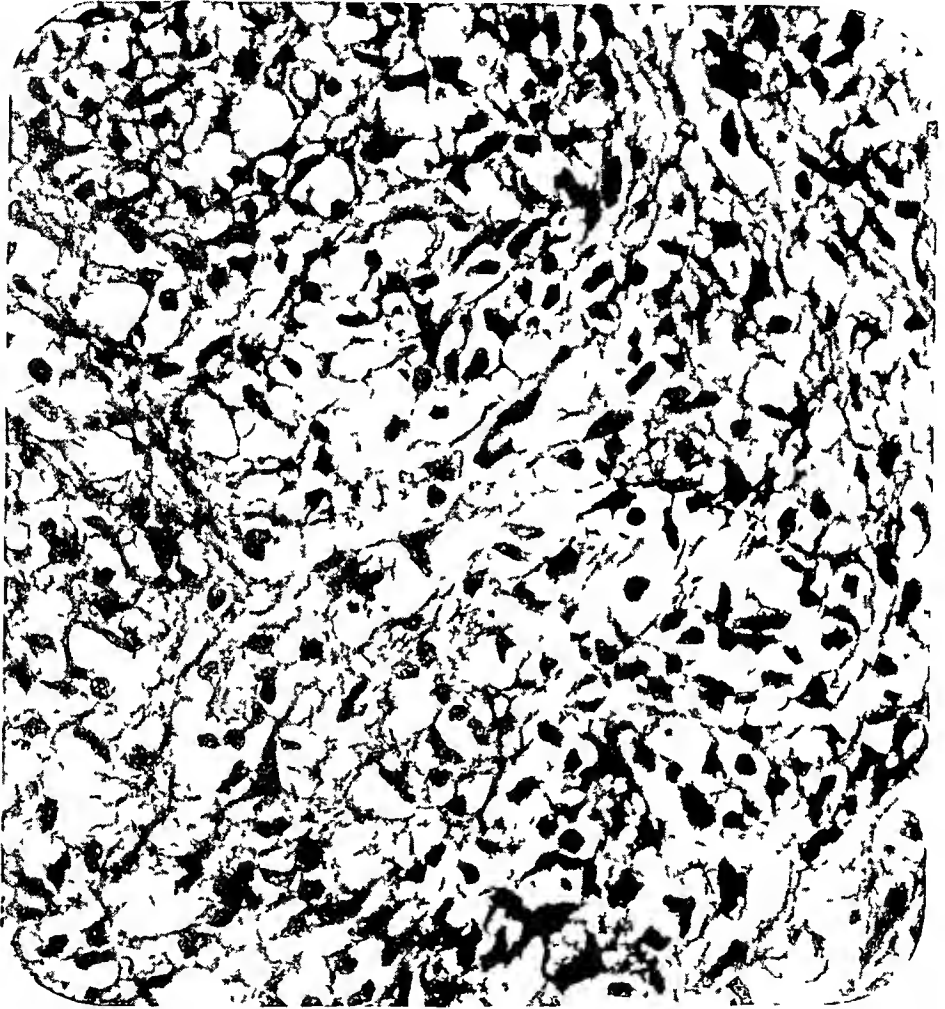


FIG 3 Case 1 Histological picture of xanthoma cells in an excised tendon xanthoma of the hand

tendon sheath xanthomata are named the "gout form of xanthomata" even in later publications and textbooks. "Gout form" is a misleading term in these cases. True gout is due to a retention of uric acid and a deposit of its sodium salt in the gaps of connective tissue leading to nodules as the result of inflammatory reactions. Xanthomatous nodules are not produced by a deposit of cholesterol outside the cells, but by a disease of certain cells which contain cholesterol intracellularly. These cells undergo destruction due to their abnormal contents, and a granulomatous scar remains. Besnier called such a new growth "Xanthoma en tumeur." In 1882

Startin¹²⁷ reported six cases. In 1889 G. Lenzen and K. Knauss⁶² presented the first good pictures of such a patient in Virchow's Archiv. Brachet-Monnard,²⁰ Poensgen,^{89, 90} Balzer,¹⁰ Richter,⁹⁹ Lowe,⁶⁵ Arning and Lippman,^{6, 7} Ganat,⁴³ Ochs, Schmidt,^{107, 108} Schonheimer,¹¹⁵ Buerger,²⁵

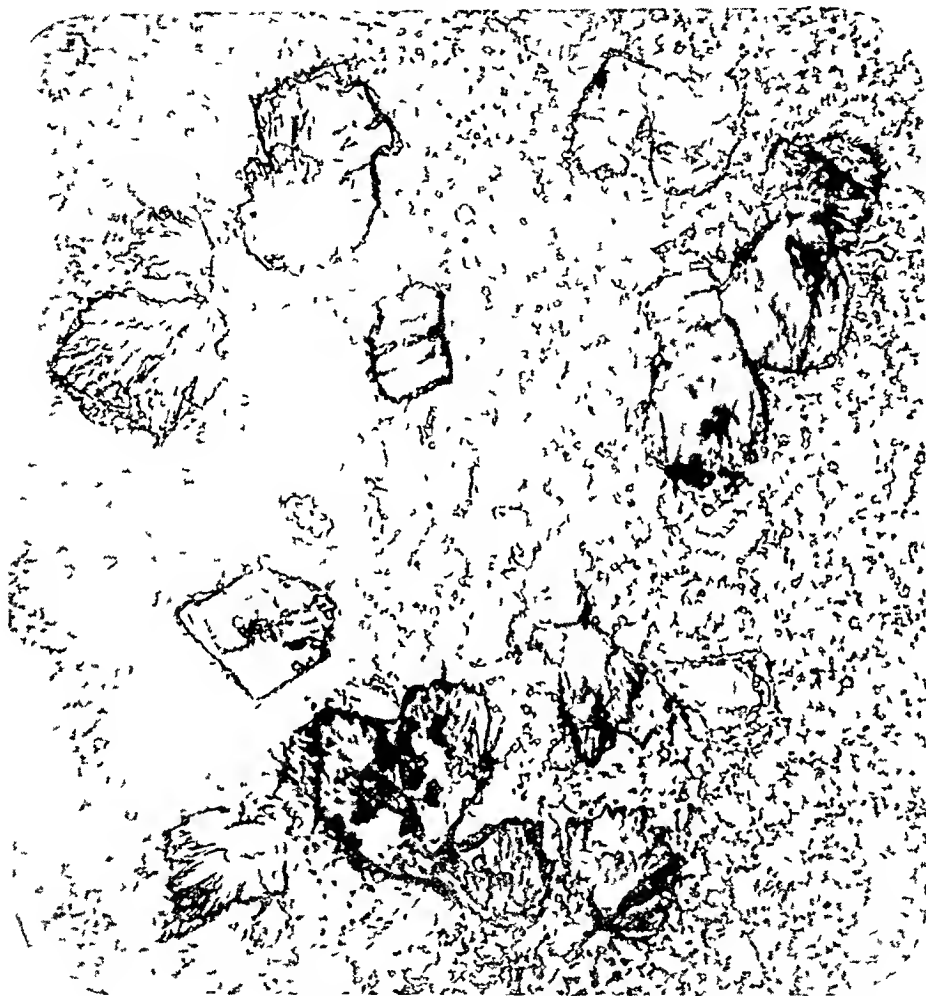


FIG 4 Case 1 Cholesterol crystals in a softened part of a tendon xanthoma

Raeder,⁹⁶ Wile,^{156, 157} and many others described such cases. In the surgical literature Beekman,¹⁵ Brochard,²¹ Buxton,²⁶ Janick,⁵⁵ Dean Lewis,⁶⁴ Romiti,^{99a} Ragins,^{96a} F. Young and C. T. Harris,¹⁵⁹ emphasized the fact that xanthomata of the tendons are part of the tendon. Thus they cannot mechanically be separated from the tendon.

One of the tendon sheath xanthomata of our Case 1 was excised by Dr. Levenson for chemical analysis. The nodule could only be partially removed because the tumor was a part of the tendon of the third finger of the right hand.

Comment Sister and brother (Case 1 and Case 2) are elderly persons

In the sister the first tendon sheath nodules developed at the age of 35, the tumors on the Achilles tendons at the age of 55. The brother first noticed nodules on his hands at the age of about 40. The name "xanthoma juvenile" sometimes used in the literature for the xanthomatous tendon sheath is therefore not justified, although in many cases the development starts in



FIG 5 Case 2 Xanthomatous nodules of the tendon and tendon sheaths of the hand

the first years of life and even a congenital case has been reported. It is noteworthy that both our patients showed no other xanthomata of the skin although the tendon sheath xanthomata had been present for almost 30 years. The pinhead sized xanthelasma at the pressure point of the spectacles on the nose developed only recently.*

Histological Findings The main piece of tissue consisted of young fibroblasts and granulomatous tissue. This granulomatous tissue in which giant cells were found, invaded the normal tendon. Large cells with one or two nuclei were scattered throughout the nodule. These cells with a foam-like opaque protoplasm (foam cells) contained fat, cholesterol and cholesterol esters and monoaminophosphatide. The foam cells are found massed in the reticular tissue. They are supposed to develop from reticulum cells and histiocytes. The characteristic picture of a xanthoma, where it may be encountered, consists of scattered or aggregated large foam

* While this paper was in press, two papers appeared, one by L. van Bogaert, H. J. Scherer, and E. Epstein^{19a} with the title "Une forme cerebrale de la cholesterinose generalisee" and the other by E. Epstein and K. Lorenz^{25a} describing a similar case. These cases of van Bogaert, Scherer and Epstein showed severe neurological disturbances, ataxia, atrophies of different groups of muscles, disturbance in speech. Later on bulbar symptoms and flaccid paralysis of all extremities developed. The neurological symptoms began at the age of 12, progressed until the age of death, of 40 years. At the age of 33 only tendon xanthomata developed. Excellent histological pictures show foam cells and deposits of cholesterol crystals in the central nervous system. None of our cases with tendon xanthomata (1, 2, 7, 9, 10, 11, 12, and 13) showed any psychic or neurological abnormalities. The cases of van Bogaert showed normal and high normal serum cholesterol like our cases 2 and 10. The combination of central nervous system xanthomatosis and tendon xanthomata has not been described until now.

cells occurring in granulomatous tissue with fibroblasts and exudate cells or in old connective scar tissue

One area of the excised nodule, the size of a pinhead, was softened. Microscopically the yellow detritus showed typical cholesterol crystals and a few needles, probably cholesterol esters.

Chemical Findings The cholesterol content in the serum of Case 1 was never extremely high. However, figures above 400 were observed. Our early observations on this patient showed an inverse ratio of cholesterol-cholesterol esters. During the period of the cholesterol-poor diet, a normal ratio was restored but the total cholesterol remained at the same level, despite a cholesterol-poor diet taken over a long period of time. The brother, who had smaller nodules, exhibited high normal total cholesterol but an inverse ratio of cholesterol-cholesterol esters. In the cases of tendon xanthomata described in the literature, the total cholesterol values are very high and the cholesterol esters especially are increased. The inverse ratio of cholesterol-cholesterol esters suggests an involvement of the liver although clinical signs of hepatic disease are absent. Neither patient was ever jaundiced. It is significant that despite the patients' ages no unusual signs of vascular disease were found.

‡ In this and in most of the later described cases of xanthomatous diseases, phospholipids are determined quantitatively. Monoaminophosphatides (lecithin-cephalin) and diamminophosphatides (sphingomyelin) are determined separately by our new method (Thannhauser and Setz¹³⁵). Up to the present time the phosphorus value obtained using Bloor's method was multiplied by 25 and the figure thus obtained designated as lecithin. However, the so-called lecithin value comprises the monoaminophosphatide (lecithin-cephalin) and diamminophosphatides (sphingomyelin). Not only are these substances notably different in their chemical constitution, but also in their physiological significance. With our method of precipitating the sphingomyelin complex as Reinecke compounds, and separating and weighing the sphingomyelins, it is possible to determine sphingomyelins gravimetrically and to evaluate the rest of the formed total lipid phosphorus as lecithin and cephalin. Using serum from patients suffering from xanthomatous diseases, this method demonstrates whether an increase of cholesterol in the serum and tissue is accompanied by an increase of monoaminophosphatides (lecithin-cephalin) or by an increase of diamminophosphatides (sphingomyelin) or by a simultaneous rise of all three lipids.

In the serum of Case 1 the total phospholipids were increased. It is shown that the increase of phospholipids results mainly from a rise in the monoaminophosphatides (lecithin-cephalin). The sphingomyelins show only a small rise. In the analyzed tissue of the tendon sheath xanthoma, there was considerable increase of cholesterol and monoaminophosphatides but only traces of diamminophosphatides could be detected. These findings demonstrate that in the examined case an increase of sterols in the serum

as well as in the tissue is combined with an increase of monoaminophosphatides (lecithin-cephalin) but not with an appreciable increase of sphingomyelins. The physiological significance of this finding is unknown, but clinically it is important that the xanthomatous diseases show, in addition to the outstanding symptoms of increased cholesterol in serum and tissue, increased monoaminophosphatides, while in Niemann-Pick's disease the outstanding finding is increased diaminophosphatides (sphingomyelin) (E Klenk¹³)

XANTHOMA TUBEROSA

Case 3 Female of 40 years had known she had diabetes for two years. Had taken no special diet. Sugar excretion was always around 1 per cent (10 to 20 gm) daily. She noticed peculiar "warts" of yellowish color on both elbows five years previously. Blood examination showed slight lipemia. On both elbows there were typical xanthomata tuberosa. She became sugar-free on diet, but the tuberous xanthomata did not disappear. Total cholesterol 570 mg per cent.

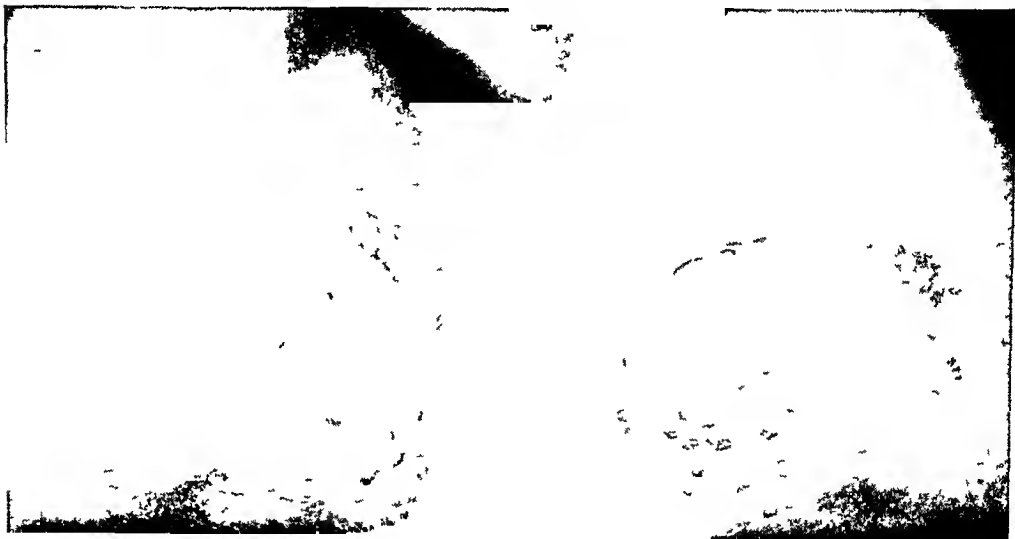


FIG 6 Case 4 Xanthomata tuberosa on both elbows

Case 4 The patient is a 30 year old physician suffering from chorioretinitis of the disseminated type, affecting both eyes. He had had difficulty with his vision for three years. Despite search, a definite etiology could not be found. At almost the same time he noticed small lesions about the elbows, knees and buttocks which were diagnosed as xanthomata tuberosa. His main complaint was fatigue for the previous three years. He had no fever, no loss of weight. His appetite was good and he carried on his profession satisfactorily. Two children were living and well. Physical examination revealed no vascular disease. Blood pressure 110 systolic and 90 diastolic. Urine findings negative.

On both elbows there were xanthomata tuberosa. The pea-sized xanthomata had a yellow color and marked hyperkeratosis on the top of the lesions. Similar lesions were found on the knees and on the buttocks. No other xanthomata were observed. Mucous membranes were free.

The creases on the palms of both hands were yellow, of a carotene-like color. His blood serum showed the same color due to carotinemia. Quantitative determination of carotene was not carried out at this time.

Blood sugar (fasting) 86 mg %
 Sugar tolerance curve, 7/7/36 Fasting 86 mg %, $\frac{1}{2}$ hour 154 mg %, 1 hour 102 mg %, 2 hours 78 mg %, 3 hours 53 mg %, 4 hours 93 mg %

This rather flat tolerance curve does not suggest a latent diabetes

Serum	Van den Bergh	0 542 (Direct, negative)
	Total fats	1088 mg %
	“ cholesterol	476
	Free “	125 (Normal ratio, free esters)
	Cholesterol esters	351
	Sphingomyelins	243 (Normal 100 to 150 mg %)
	Total phospholipids	437 (Normal 200 to 350 mg %)
	Monoaminophosphatide, total lipids—diaminophosphatide	194 mg %
	(Normal 100 to 150 mg %)	
Analysis of stromata of red blood cells		
	Diaminophosphatide	3 7 mg %, low normal (Normal 4 to 5 mg %)
	Total lipids	10 6 “ “ “ “ (“ 10 to 15 “ “)

Comment We have thus far considered only simple forms of what we consider to be xanthomata tuberosa. The above described nodules of the tendon sheaths as well as xanthomata multiplex disseminata, which will be illustrated later, are erroneously designated as xanthomata tuberosa. Tuberos xanthomata are nodular elevations of the skin. The nodules are usually observed isolated, not confluent or aggregated in small groups. The shape is irregular and they may vary from pea size to the size of a chestnut. Their favorite location is the extensor surface of the arms, especially the elbows, or on the buttocks. The surface usually shows hyperkeratosis and is of yellow or carrot-like color. Xanthomata tuberosa and xanthomata disseminata which are entirely different in size, shape, color and localization are generally confused in the literature. The mucous membrane and larynx are rarely involved in tuberos xanthomata in contrast to the xanthomata multiplex disseminata in which lesions almost always arise simultaneously in the mouth and larynx.

The reason for this confusion may be due to the fact that the histological findings are identical in both xanthomata tuberosa and xanthomata disseminata despite the fact that appearance and localization are clinically entirely different. In both lesions we find foam cells, i e, cells with one or two nuclei, “Touton giant cells”. The amount of fibrous tissue which is found in the nodule surrounding the foam cells varies according to the age of the xanthomatous nodules. In later stages only granulomatous scar tissue may be found. There is no sign of inflammation or vascularization around the nodules on the skin and no papule or pustule formation. This is important in differentiating between xanthomata tuberosa and the eruptive form of papulo-pustular lesions which occur in severe diabetes and symptomatic hypercholesteremia.

Xanthomata tuberosa may be combined, as in Case 3, with mild diabetes. In these cases of rather mild diabetes the lesions of xanthomata tuberosa (which do not itch) may be the expression of a similar xanthomatous eruption in the pancreas. In 1921 Wijnhausen¹⁵⁴ was able to verify such a coincidence by operation. In his patient xanthomata tuberosa were noticed

34 days before sugar was found in the urine. Frequent attacks of ileus, as in bowel obstruction, accompanied by fever were observed. Operation one year after the onset of the symptoms revealed chronic pancreatitis and tuberous xanthomata in the pancreas. The patient recovered from the operation. The diabetes and the tuberous xanthomata of the skin may be considered the result of the same disease, i.e. xanthomatosis, affecting the skin and pancreas simultaneously. This suggestion has also been mentioned by Rowland.¹⁰¹ As early as 1880 Gendre⁴⁵ reported the case of a patient who had been suffering from mild diabetes and tuberous xanthomata for 10 years. "Malgré la présence du diabète sucré datant de dix ans ce cas ne peut pas être rangé parmi les xanthomes diabétiques."

The eruptive form of papulo-pustular xanthomata, the so-called xanthomata diabeticorum, is entirely different in etiology from the xanthomata tuberosa. Xanthomata diabeticorum are the sequel of a severe diabetes mellitus in the course of which lipemia and hypercholesteremia occur, occasionally producing the itchy papulo-pustular eruptions which appear and disappear.

I should like to emphasize further the importance of differentiating between xanthomata tuberosa and xanthomata disseminata because the visceral organs involved may be predicted by the kind of skin lesions present. Xanthomata tuberosa and plana may be combined, as we shall see later, with endocardial and vascular xanthomata as well as with hepatic and pancreatic disease, while xanthomata disseminata is found with xanthomata of the bones and lungs, xanthomata of the brain and diabetes insipidus.

Serum Chemistry. The serum of a patient with xanthomata tuberosa shows high total cholesterol values largely due to increased cholesterol esters. The cholesterol-cholesterol ester ratio is normal or changed in favor of the esters. The monoaminophosphatides (lecithin-cephalin) are markedly increased. The diaminophosphatides (sphingomyelin) are also a little higher than normal but the monoaminophosphatide-diaminophosphatide ratio shows that the increase of total phospholipids is mainly due to the increase of lecithin-cephalin. The glycerides are also considerably increased. The increase of the monoaminophosphatides and glycerides simultaneously with the cholesterol is to be considered a fact evident from many observations.

"FORME FRUSTE" OF XANTHOMATOUS DISEASES

Case 5. Mrs. F., 55, main complaint fatigue. For many years easily tired, very active in the household. Physical examination. Mentally quick, haggard lady. The color of her skin is brownish, like a tan (has not exposed herself to sunlight). Both palms of hands and feet and especially the creases of the hands show xanthosis, that is, a yellowish carotin-like color. Sclerae normal color. There are no abnormalities of the inner organs discovered, no signs of hypothyroidism. Urine and blood normal. Basal metabolic rate, minus 10 per cent, blood sugar 85 mg per cent, bilirubin, van den Bergh 0.5, icteric index 11.

	Total Cholesterol	Free	Esters	Total P Lipid	Diaminophos Sphingomyelin	Monoamino-p Lecithin-Cephalin	Fat
9/24/35	295 mg %	103 mg %	192 mg %				
After cholesterol poor diet	276 mg %	75	201	290 mg %	81 mg %	209 mg %	389

Case 6 E de S, 48 years Family History Diabetes in several members of his ancestry Patient has six healthy children Patient reports that 10 years ago he had a trace of sugar in the urine Sugar disappeared without keeping to diet Six years ago he was examined in Paris and hypercholesteremia was found without other symptoms Total cholesterol at this time was 455 mg per cent Four months later, after a diet poor in fats, the total cholesterol was 320 mg per cent Patient kept on this diet for six years Cholesterol determination repeated several times during the past year showed values of total cholesterol around 200 mg per cent Basal metabolic rate normal on several occasions

The main complaint of the patient is fatigue He is sometimes depressed and feels uneasy He lives in the tropics now, has to be very active in his business His mental agility is quick, in contrast to his physical fatigability

Physical findings Man of normal figure, no signs of hypothyroidism The skin exhibits xanthosis on the trunk as well as on the extremities (see case 4), especially the palms of the hands and feet and the creases on the palms show a yellowish carotene-like color The lungs are normal Heart is normal in size, systolic murmur at aorta Blood pressure 135 systolic and 85 diastolic Liver and spleen not remarkably enlarged Blood and urine normal Blood sugar 102 mg per cent, bilirubin (Van den Bergh) 0.5 mg, icteric index 20

Blood chemistry

Total cholesterol	Free	Esters	Total P Lipid	Diaminophos Sphingomyelin	Monoamino-p Lecithin-Cephalin
216 mg %	50 mg %	166 mg %	309 mg %	112 mg %	197 mg %

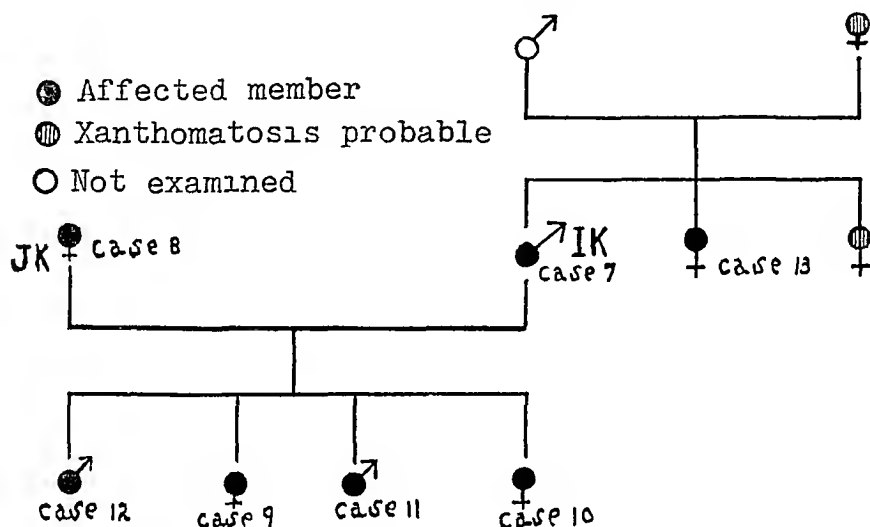
We report these cases as "forme fruste" of xanthomatous diseases because they have the same features as patients exhibiting xanthomata tuberosa (hypercholesteremia, xanthosis (carotinemia), inclination to mild diabetes) but no skin xanthomata These patients are often diagnosed as hypothyroids because they exhibit physical fatigability, high blood cholesterol and sometimes basal metabolic rates on the lower borders of normal In contrast to patients suffering from hypothyroidism, these patients are mentally very alert, they are not anemic, they perspire easily and have a smooth skin They are not slow in their activities, but they fatigue easily The cases reported by Edelmann^{34a} with xanthosis, fatigability, diffuse pains in muscles, complaints of irritability of the gastrointestinal tract, belong to this group We determined the carotene content of the serum quantitatively in a case which we have seen recently and found 0.4 mg per cent (normal 0.05 to 0.1 mg per cent) We believe that the forme fruste of xanthomatous diseases, characterized by hypercholesteremia, xanthosis and caroti-

nemia, associated with fatigability and inclination to mild diabetes, is seen not infrequently if distinguished from hypothyroidism

XANTHOMATA TUBEROSA AND PLANA AND TENDON XANTHOMATA

We were fortunate to discover an entire family suffering from xanthomata of the skin as well as of the tendon sheaths G K, a female child (Case 9), aged 11, was observed at the Children's Hospital We are indebted to Dr Blackfan and Dr Diamond for the privilege of seeing this child and for the opportunity to study the entire family, whose case histories follow

FAMILY TREE OF FAMILY K



Case 7 Mr I K, 50 years old, male, Jewish plumber, noticed painless swellings on knuckles of both hands when he was about 30 years old. During the last 5 to 10 years he also noticed swellings develop on both heels. Two to three years ago, he first suffered from attacks of substernal pain which were diagnosed as angina pectoris and responded to treatment with nitroglycerin.

He was the father of four children, all of whom showed evidence of xanthomatosis (see family tree), his mother had brown swellings on the eyelids, one sister (Mrs Ch, Case 13) had xanthomata of tendons, another sister is supposed to have xanthelasma.

He was moderately obese, not jaundiced. His eyelids showed no xanthelasma. Lungs and heart were found to be normal on physical examination. Electrocardiogram normal. Liver and spleen not definitely enlarged.

On the third, fourth and fifth fingers of both hands, xanthomata, movable with the tendons on the extensor side, were visible, most pronounced on the first interphalangeal joint. Small nodes were present in the olecranon region. Extensive swellings in the region of the lower third of both lower legs, bulging posteriorly and laterally in the region of the Achilles tendons. These swellings were firm, non-tender, larger than those in any other member of his family, measuring 8 by 3 cm.

Serum total cholesterol	265 mg %
Free cholesterol	105
Cholesterol esters	160
Total phospholipids	450 mg %
Diaminophosphatide	150 mg %
Monoaminophosphatide	300 mg %
Fat as fatty acids	496

Case 8 J K, a 47-year-old Jewish housewife, first seen October 27, 1936, noticed brownish swellings on both upper eyelids at the age of 23, after her first child was born. When she was 40 years old these lesions had grown considerably and similar lesions had appeared on both lower lids also. No history of serious illness in the past.

Family history See family tree

She was a markedly obese woman without icterus. There were characteristic xanthelasmata in both upper and lower eyelids, the smaller measuring 3 mm in diameter, the largest 5 by 20 mm, of soft consistency, elevated 1 to 2 mm above the level of the skin. No tumors of any tendons were palpable. Liver and spleen were not palpable and not enlarged on percussion.

	10/30/36	11/2/36
Serum total cholesterol	482 mg %	533 mg %
Serum free cholesterol	129	129
Serum cholesterol esters	353	404
Total phospholipids		394
Diaminophosphatide		132
Monoaminophosphatide		262
Fat as fatty acids		585

On a reduction diet, she lost 31 pounds in seven months. There was no change in her xanthelasma.

Case 9 G K, 11 years old, Jewish schoolgirl (daughter of J K) noticed painless nodes appear in the region of both heels at the age of seven. One or two years later similar lesions were seen on the knuckles of several fingers and there was also involvement of the skin of the knees and elbows.

She was an underdeveloped, undernourished, intelligent girl. The xanthomata of the skin were round, brownish-orange colored, flat lesions, 3 to 4 cm in diameter, with somewhat pronounced margins and sharp borders. The center of these lesions was darker and slightly depressed. Similar, although much smaller tuberosus skin lesions were visible in the gluteal folds and flexor aspect of the knees. Besides there were xanthomata of the extensor tendons of the third and fourth fingers of both hands, and larger xanthoma nodes in both Achilles tendons. Liver and spleen not felt. No jaundice. (Figures 7, 8, 9, 10, 11)

10/26/36	Serum total cholesterol	667 mg %
	“ free “	203
	“ cholesterol esters	464
	Total phospholipids	448
	Diaminophosphatides	194
	Monoaminophosphatides	254
	Fat as fatty acids	423
3/27/37	After moderate restriction of animal fat containing food	
	Total cholesterol	785 mg %
	Free “	222
	Cholesterol esters	563

The round intradermal lesion on the left elbow was surgically removed and proved to be in intimate contact with the tendon of the triceps muscle. Tissue analysis of the dried lesions, freed as much as possible from subcutaneous fat, showed no sphingomyelin. The total phospholipid content of the dried substance was 12.7 mg per cent. Total cholesterol of the dried substance was 13.1 mg per cent.

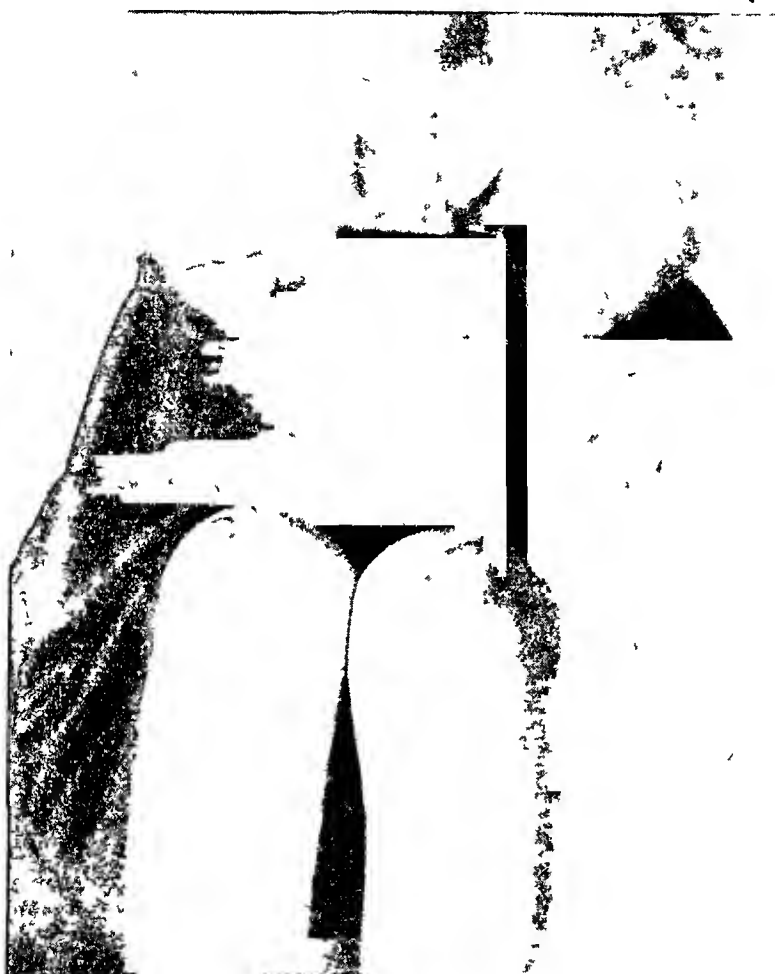


FIG 7 Case 9 Xanthomata tuberosa and plana on both elbows and both knees

Case 10 S K, 22-year-old Jewish girl, daughter of J K, was seen December 7, 1936. She had no complaints but had seen and felt nodes on her heels for two years. She had been obese as a child.

Patient showed slight bulging of the region of the Achilles tendons on both sides, 5 cm distant from the floor, as the only demonstrable abnormality.

Total cholesterol (serum)	244 mg %
Free cholesterol	83
Cholesterol esters	161

Case 11 A K, 16-year-old Jewish schoolboy (son of J K) had no complaints. He showed xanthomata of various extensor tendons of the fingers of both hands and also of both Achilles tendons.

Serum total cholesterol	282 mg %
" free "	97
" cholesterol esters	185
Total phospholipids	303
Diaminophosphatide	137
Monoaminophosphatide	166
Fat as fatty acids	354



FIG 8 Case 9 Xanthomata tuberosa on the buttocks

Case 12 H K, eldest son, 23 years old, student, healthy, no complaints or pathological findings in lungs or heart, normal blood pressure, normal liver and spleen Examination of left Achilles tendon reveals a pea-sized tendon xanthoma, similar to those of his brother and sister Chemical findings in the serum Icteric index 13, Van den Bergh less than 0.5 mg per cent, carotene 0.25 mg per cent

Total cholesterol	400 mg %
Free cholesterol	100
Cholesterol esters	300
Fat as fatty acids	471

Case 13 Mrs Ch (sister of Mr K), 51 years old, Jewish housewife (aunt of the 4 K children) was seen April 17, 1937 She had noticed painless lumps on knuckles of various fingers at the age of 37

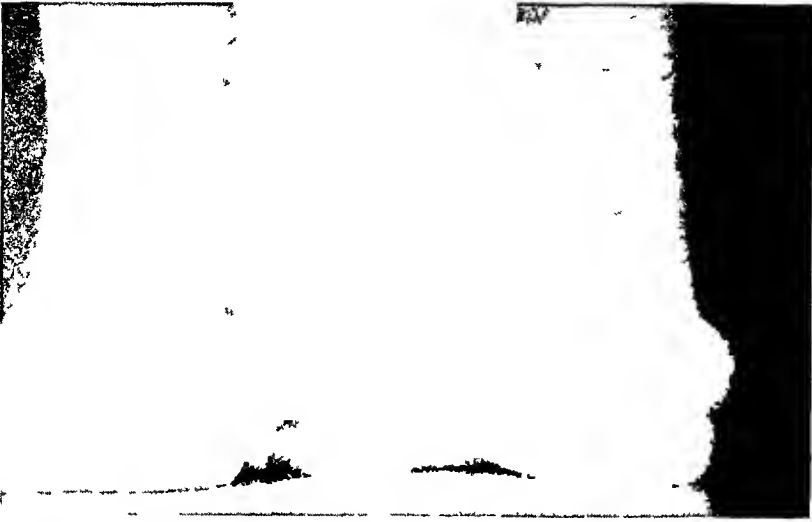


FIG 9 Case 9 Xanthomatous nodules on both Achilles tendons



FIG 10 Case 9 Xanthoma planum, Sudan staining

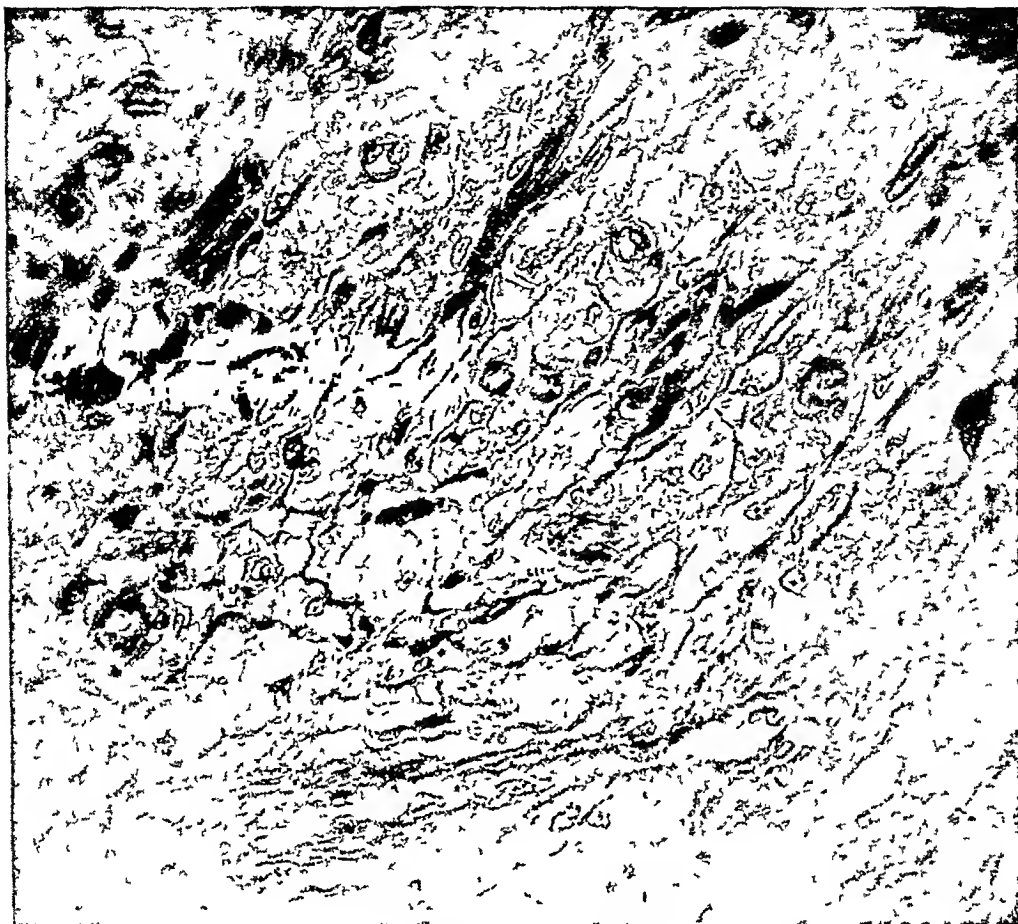


FIG 11 Case 9 Xanthoma planum xanthoma cells

She was moderately obese, showed no icterus, no xanthelasma of the eyelids. There were xanthomata of three fingers of each hand, predominantly in the region of the phalango-metacarpal joint, also xanthomata in both Achilles tendons, 2 cm in diameter and small superficial tuberosus nodules in the region of both elbows. Liver and spleen were not enlarged.

Serum total cholesterol	500 mg %
" free "	183
" cholesterol esters	317
Total phospholipids	632
Diaminophosphatides	83
Monoaminophosphatides	549

Comment Heredity Case 8 has unusually extensive xanthelasma on both eyelids. Several members of the father's (Case 7) family have tendon sheath xanthomata. All the children of this couple were examined and all were found to have tendon sheath xanthomata. The youngest child, Case 9, has xanthomata plana (xanthelasma), xanthomata tuberosa and tendon sheath xanthomata. It is evident from different cases described in the literature (Torok,¹⁸⁸ Raeder,⁹⁶ Wile and Dumehing,¹⁵⁷ and from the family tree of this family that heredity is dominant.

Case 9 (11 year old girl) has different kinds of xanthomata of the skin. Later we shall discuss the fact that histological examinations of all kinds of xanthomata reveal a more or less uniform histological structure consisting of foam cells and granulomatous tissue. Because the gross appearance of xanthomata of the skin is different in shape and in color, we have to deal with a nomenclature which describes the different gross appearances of the skin but not different diseases.

Xanthomata plana or xanthelasma are flat xanthomata of carotene-like color or that of chamois leather. In the child, Case 9, xanthomata plana were found on both elbows * both knees and buttocks. In addition she had xanthomata tuberosa on both elbows, on the buttocks and on the skin of the heels overlying the tendon tumors. Temporarily when she was first observed and once later she even had an eruptive papulo-pustular form of xanthomata on both arms and legs. These eruptive lesions appear and disappear and up to the present time have been observed only on patients suffering from diabetes mellitus.

Later we will show that the papulo-nodular eruption known as xanthomata diabeticorum may occur without diabetes not only in cases such as that just described but also in patients with jaundice and xanthelasma due to xanthomatous liver cirrhosis with a very high serum cholesterol.

We follow Montgomery and Osterberg ⁷⁶ in separating xanthomata multiplex disseminata from the discussed manifestations of xanthomata of the skin. The disseminated multiple xanthomata does not differ in its histological structure but differs in shape, color and especially in localization, distribution and diagnostic significance. We were unable to find a single case in the literature where disseminated multiple xanthomata of the skin were found in the same patient coincidentally with xanthomata plana and tuberosa, or in patients with tendon sheath xanthomata. But, as we observed in the members of the K family and other cases cited in the literature, xanthomata plana as well as xanthomata tuberosa are very often combined with xanthomata of tendons.

DISCUSSION OF COINCIDENCE OF XANTHOMATA PLANA AND XANTHOMATA OF TENDONS WITH XANTHOMATOUS INVOLVEMENT OF HEART, BLOOD VESSELS, AND LIVER

In 1879, Calcutt Fox,³⁹ in the first description of tendon sheath xanthomata combined with xanthomata plana, found the mitral valve involved with xanthomata. Poensgen (1887)⁸⁹ describes tendon sheath xanthomata, xanthomata plana and tuberosa with aortic involvement in a boy of eight years. Lenzen and Knauss (1889)⁶² described and showed a picture of an 11-year-old girl, who, like our patient of the same age (Case 9), had xanthomata plana, xanthomata tuberosa and tendon sheath xanthomata. Their patient died from an intercurrent infection following operation. Autopsy

* We are indebted to Dr. Hilbert F. Day for the excision of one xanthoma plana on the left elbow. 1½ years after this excision there is no recurrence of the xanthoma in the scar.

revealed xanthomata on both pulmonic and mitral valves (patient exhibited intra-vitam unusually loud systolic murmurs) and xanthomatous patches in the pulmonary artery, but the aorta and left carotid showed a xanthoma of the intima simulating a neoplasm which almost occluded the lumen of the vessel. Both coronaries of the 11-year-old child also demonstrated xan-



FIG 12 Xanthomatous nodule of the intima of an artery (Microphotograph of Dr Timothy Leary of Boston)

thomatous patches the size of a pinhead. It is noteworthy that this patient had a sister with the same disease. Similar familial cases with involvement of the heart and the arteries in children are described by Arning (1910),^{6,7} and by Lowe (1910)⁶⁸ and then by Hess (1934)⁵¹. In all these cases the xanthomatous involvement of the endocardium and vessels was combined with tendon sheath xanthomata and skin lesions of xanthomata plana and xanthomata tuberosa. We should like to emphasize that in the literature, as far as has been able to be determined, not a single case is described where xanthomata multiplex disseminata was found combined with xanthomata of the endocardium and the vessels which we shall picture and discuss later.

At this point we should like to call attention to the fact that hypercholesterolemia is found where xanthomata plana, xanthomata tuberosa, and ten-

don sheath xanthomata are combined with vascular xanthomatous disease, while normal cholesterol values are found in patients suffering from xanthomata multiplex disseminata and xanthomatous bone diseases

Simultaneous involvement of the liver is rare in cases where xanthomata plana and tuberosa and tendon sheath xanthomata exist over a long period of time without jaundice. Later we shall show that jaundice is the initial symptom of xanthomatous biliary cirrhosis in the course of which (but only after a period of jaundice) the most impressive xanthomatous changes of the skin in the form of xanthomata plana or xanthomata tuberosa may arise. The spleen, the lymph glands and the lungs were not involved in this group of cases but these organs are involved in the group of xanthomata multiplex disseminata of the skin with xanthoma in the brain and the bones

XANTHOMATOUS BILIARY CIRRHOSIS

Case 14 Female, aged 35 years, wife of a farmer in Germany¹⁰⁴ One sister suffering from cholecystitis. Married, one healthy child. Patient noticed jaundice in January 1931, for the first time, no pain or other symptoms from the gall-bladder, stools clay-colored, urine dark, itching all over the body. The physician diagnosed gall stones and the patient was operated upon on April 7, 1931. The wall of the gall-bladder was very thick. A gland was found which was intimately connected with the gall-bladder (xanthomatous scar tissue) in the place where the hepatic duct branches. The liver was firm in consistency. There were no stones found and all the larger bile ducts were free of stones. The gall-bladder was removed. After the operation the jaundice increased. Patient grew worse. Treatment with diathermia and carbohydrate and insulin was without effect. Operation again considered by the physician. She was then first admitted to our hospital, November 19, 1931. Weight 52 kg, height 148, severely jaundiced. Several lesions of the skin from scratching. At that time no xanthomata or tuberosus xanthomata. Temperature between 37.1° and 37.9° C. Lungs. Normal vesicular breathing, no dullness. Heart. Normal size, no murmurs, blood pressure 140 systolic and 80 diastolic, pulse 76. Abdomen distended, umbilicus deformed. Liver enlarged, five fingers below the costal margin, very firm, surface smooth. Spleen enlarged, firm. There is a small amount of ascites. No *caput medusae*. Urine trace of albumin, no sugar, urobilin and urobilinogen strongly positive, bilirubin positive, sediment, few leukocytes. Blood 75 per cent hemoglobin, 3,600,000 red blood cells, 7,200 white blood cells, 1 basophile, 1 eosinophile, 1 stab form, 70 polynuclears, 27 lymphocytes.

Hospital treatment from November 19 to December 20, 1931. Carbohydrate-rich, protein-poor diet with 5 units insulin twice daily. Diathermia of the liver. Weight loss during this time 0.5 kg. From November 26 to December 8, very strong menstrual bleeding. On December 11, sudden rise in temperature to 39° C, fever continued for five days. Jaundice during the hospitalization was not changed, never evidence of complete obstruction. Never colicky pain. Discharge diagnosis Biliary liver cirrhosis.

Second admission to our hospital January 11, 1933. Patient reports that no marked changes have occurred since her hospital stay. The menstrual bleeding in the meantime was always excessive. She was inclined to bleeding from the gums and from the genitals apart from menstruation. She felt increasingly weak and without appetite. Stools were not completely acholic. Urine always dark. Physical examination. Weight 43 kg. Jaundice deeper brown. Liver, much larger than at the first admission, almost the whole abdomen is filled by the liver. Its border is

three fingers below the umbilicus Very firm, surface smooth, no nodules Spleen the same size as at the first admission, three fingers below the left costal margin No ascites was found at this time Surprisingly large lemon-yellow patches were visible on the green-brown jaundiced skin which had not been present the year before These yellow patches, varying in size from 1 to 10 cm, easy to recognize as xanthomata plana, were found around the eye-lids, on the nose and cheeks, on the abdomen



FIG 13 Case 14 Xanthoma plana on both eyelids, the nose and the face

and also on the scar from the operation On the arms both on the flexor and extensor surfaces and all over the body were extremely itchy papulo-pustular nodules Around the nodules was a small inflammatory zone of pink color which changed peripherally to bluish-red and finally to brownish The pustules did not contain fluid or pus but on opening, a soft tissue of yellowish color was seen Because these



FIG 14 Case 14 Eruptive form (papulo-pustular form) of xanthoma.

eruptions itched so excruciatingly they had been badly scratched and give the impression of an abraded vesicle with the formation of a crust. The nodules which were not injured by scratching healed without crust formation, but a dark pigmentation remained. Blood: 55 per cent hemoglobin, 2,600,000 red blood cells, 9,000 white blood cells, blood sugar 82 mg per cent. Bilirubin direct 14.1, indirect 8.1 Van den Bergh's units. Total cholesterol 657 mg per cent, free cholesterol 376 mg per cent, cholesterol esters 281 mg per cent. Urine: Albumin positive, sugar negative, urobilinogen strongly positive. After a period of strict vegetable diet without any animal cholesterol we noticed an impressive decrease of the total cholesterol, but the inverse ratio of cholesterol-cholesterol esters remained, which is according to Thannhauser and Schaber a sign of liver damage.

	Total cholesterol	Free cholesterol	Cholesterol esters
February 1	657 mg %	576 mg %	81 mg %
February 14 (cholesterol free diet)	406	314	92
February 28	152	132	20

On a less strict diet which contained some animal sterol the patient showed after four weeks 296 mg per cent total cholesterol, 124 mg per cent free cholesterol, and 72 mg per cent cholesterol esters. Normal persons who eat a diet free of animal sterol do not change their blood cholesterol (Bareda¹¹). Within 28 days the total cholesterol in this patient's case decreased from 657 mg per cent to 152 mg per cent. These figures show that 20 gm of cholesterol disappeared from the blood if we take four liters as the normal amount of circulating fluid. During the vegetable diet period the sterols in the feces were isolated and determined following the technical methods of Schonheimer. The daily amount of sterol in the feces in the beginning of the diet was 1.26 gm, later it fell to 0.53 gm, and at the end of the diet to 0.827 gm. The attempt was made to isolate cholesterol, dihydrocholesterol and coprosterol quantitatively. Only traces of coprosterol were found but it was impossible to isolate free cholesterol or dihydrocholesterol from the feces during this period. This result is in conformity with the findings of Schonheimer. The sterol structure present in the feces while on the sterol-free diet consists apparently only of plant sterols. It is not evident how the 20 gm of cholesterol disappeared from the blood. Bacterial destruction of cholesterol in the feces may give an explanation for this important fact according to B. Ottenstein.

The patient grew gradually weaker. She again developed a high fever for the period of a few weeks. Her weight fell to 41 kg. She lost ground rapidly and died eight weeks after she left the hospital. A partial autopsy was performed. Prof. Aschoff, who examined the liver, found a marked cirrhosis and the same xanthomatous changes of the liver tissue which Chvostek described in his case of "xanthelasma and icterus" as xanthoma of the liver.

Case 15 (I am very much indebted to Dr. James Waring, Professor of Medicine of the University of Colorado, for the permission to publish this case.)

H. L., housewife, aged 32 years, born in Vienna. Entered Colorado General Hospital November 19, 1935, with the complaint of jaundice and weakness of four years' duration and of yellowish plaques distributed over the body, especially on the face and in the creases of the hands and feet, of about two and a half years' duration.

Past history Patient had measles at seven years, chickenpox at eight years. Never has had scarlet fever, mumps, whooping cough, rheumatic fever, chorea, or venereal disease. Menstrual periods started at 15 years, were regular every 28 days.

until spleen was removed two years ago Has not menstruated since No menopausal symptoms One child, nine years of age, a boy, living and well No other pregnancies In 1926, the appendix and one ovary were removed

Family history Mother, living and well, aged 58 years No tuberculosis contacts No history of cancer, diabetes, or Bright's disease No illness in family similar to patient's No blood dyscrasias, no hay fever, no asthma

Present illness The patient believes that she was feeling quite well until June 1931 At that time she first noticed that her eyes were yellow Shortly afterwards her skin became yellow, the urine highly colored and the stools grayish in color This jaundice gradually increased in intensity and was accompanied by much itching In September 1931, she consulted a physician in Boston who told her that she had gall stones and advised an operation, which was refused Patient's weight at the onset of her illness was 160 pounds In four months, that is at the time she consulted the physician in Boston, her weight had fallen to 132 pounds In March 1932, she consulted a physician in Cleveland who told her that she had an obstruction of the gall ducts and advised an operation which was again refused Meanwhile the jaundice had increased in severity and the itching was almost intolerable In April 1932, she came to Denver and consulted two physicians A diagnosis of obstructive jaundice was made and an operation advised At this time, she was told that she had a large liver The jaundice now showed some variation in intensity and the itching lessened but the patient complained of great weakness Around both eyelids, xanthelasma palpebrarum was noted In May 1933, she went to Memphis, Tennessee, where she was operated upon and her spleen removed, but there was no change in the condition following the operation No gall stones were found, but a narrowing of the common bile duct About a month before leaving Denver in May 1933, she first noticed yellowish deposits in the creases of her hands They came on gradually but were rather diffuse in distribution from the very onset, that is, they appeared on the face and on all extremities including both elbows at about the same time About the middle of 1934, she was quite sick with high fever, increase in jaundice and some delirium In May 1935, she was given a number of fever treatments at the Colorado Psychopathic Hospital The fever treatment did not change the condition of the patient

Patient was seen again by a doctor in Denver in August 1934 She now had yellowish plaques in the creases of the palmar surfaces of both hands They were each about 2 mm wide and slightly raised They were also present on the anterior surfaces of the elbows and on the elbow tips On the extensor surfaces of the elbows the plaques were enlarged patches and were much raised above the surrounding skin They were also present over the buttocks Progress from the fall of 1935 was gradually downward She had numerous persistent nasal hemorrhages and a little fever off and on much of the time The first nasal hemorrhage occurred about 1934, lasted about 10 hours and it is estimated that about a pint of blood was lost Since this time she has had a nose bleed of more or less severity about every six weeks Epistaxes lasted from six to ten hours and were controlled with difficulty She does not bruise easily and apparently had not had any petechial spots She showed marked susceptibility to respiratory infections which were severe and prolonged With one of these she had an acute suppurative otitis media on the right side She finally died July 1936, apparently of a typical coronary occlusion

Physical examination General appearance Her entire body is jaundiced, of a dusky bronze color with a tinge of yellow apparent The coloring is diffuse and fairly uniform with no distinct patches of pigment No deformity of bony skeleton or skull No discoloration of mucous membranes Head Small nodules apparent on upper eyelids and along the inner canthi The larger of these have been removed by her physician Eyes Some patchy congenital discoloration of the iris Left

pupil larger than right Pupils react to light and accommodation Consensual reflex present No nystagmus, exophthalmos, visual disturbances or fundal pathology Conjunctiva and sclera slightly yellow Visual fields grossly normal Mouth Posterior pharynx narrow with large hypertrophied tonsils from which no pus can be expressed Chest Organs apparently normal Diaphragm high posteriorly Heart No enlargement noted Sounds somewhat distant but no murmurs detected



FIG 15 Case 15 Xanthoma plana and tuberosa on the face, around the eyelids and the papulo-pustular eruptive form associated on the face

Blood pressure 110 systolic and 70 diastolic Peripheral vessels soft, pulse regular, rhythmic Abdomen Large operative scar The liver is palpable throughout most of the abdomen Liver is slightly tender along the left margin No nodules noted No fluid detected No bulging of the flanks Back and extremities No deformity, pain, or limitation of motion On both palms along practically all the flexor creases there are yellowish nodules about 3 mm above the skin On the extensor surface of

the elbow there is a large hyperkeratotic mass of the same character. Many similar nodules are distributed along the dorsum of the foot around the toes. Mucous membranes are free from xanthomata. Besides these tuberous and plain xanthomata, a nodular pustular eruption is to be seen, of the same appearance all over the body. There are papules which are excoriated by scratching. (In the photographs this eruptive xanthomata identical with the xanthomatous eruption in cholesterolemia during diabetes mellitus is clearly pictured.) Neurological: Gait and station essentially normal. Romberg negative. Muscular strength decreased. Ability to perform



FIG 16 Case 15 Enlarged liver

coordinated movements unimpaired. No ataxia, dysmetria, past pointing, athetosis, tremors, spasticity, rigidity, dysarthria, dysphasia, Holmes rebound phenomena or adiadochokinesis. Sensory examination essentially negative. No abnormal subjective sensations other than itching. Knee jerks, ankle jerks, biceps, triceps, radial, patellar reflexes equal and hypoactive, corneal reflex present, superficial abdominal reflexes absent. No Babinski sign or confirmatories. Cranial nerves intact.

May 2, 1935. No roentgen-ray evidence of pathologic changes in bones of skull, chest, pelvis, feet or hands. No definite defects in cranial bones, changes in sella turcica or metaphyses as described in Schuller-Christian's disease.

Urinalysis: color amber, slightly hazy, acid, specific gravity 1.022, trace of albumin, no sugar. Sediment contains a few pus and epithelial cells and many

bacteria, no casts or erythrocytes Blood examination Hemoglobin 10.2 grams, erythrocytes 3.2 million per cu mm, leukocytes 12,650, polymorphonuclears 80 per cent, lymphocytes 14 per cent, monocytes 4 per cent, eosinophiles 2 per cent Blood sedimentation $\frac{1}{2}$ hour 20 per cent, 1 hour 40 per cent Serological examination Wassermann test negative Eagle flocculation test negative



FIG 17 Case 15 Xanthomata tuberosa on both elbows

Electrocardiogram showed slight left axis deviation showing definite respiratory shift Basal metabolism rate, plus 8 Blood chemistry Sugar (dextrose) 84 mg per cent, total N P N 33, total cholesterol 400, calcium 10.60 Van den Bergh test 2.66 mg bilirubin per 100 ml blood, direct reaction Icterus index 22 Fragility of red cells normal

Biopsy Removal of a xanthoma from the dorsal surface of left elbow (November 19, 1935) (Analysis of the tissue by the Biochemical Institute, University of Denver)

	% by weight of fixed tissue
Cholesterol	
Total cholesterol	1.31%
Free " "	None
Cholesterol esters	1.31%
Phospholipids	0.117%
Equivalent to 0.934% lecithin	

Case 16 E H, a 49-year-old Jewish widow, began to have severe itching all over her body at the age of 46. Shortly afterwards eruptions of a pustular character appeared, which bled after scratching. These lesions had been recurring for three years previous to admission. The patient lost 20 pounds in weight within the first year after the onset of the illness. She complained of weakness and had noticed that her urine was at times dark brown. Past and family histories revealed no significant data.



FIG 18 Case 15 Xanthomata plana on the palms and creases

When first seen she was icteric and the skin was covered with lesions of discrete varioliform character. They were less than 1 cm in diameter, on some of them the top was replaced by a crust and surrounded by an inflamed zone. They were fairly symmetrical in distribution but possibly more on back and abdomen than elsewhere. They were superficial and the old lesions represented by faint pigmentation, which persisted for some months (figures 20, 21, 22).

Heart and lungs essentially normal. Blood pressure 160 systolic, 90 diastolic. The liver reached two to three fingers' breadth below the costal margins, the spleen two



FIG 19 Case 15 Xanthomata tuberosa and plana and eruptive papulo-pustular form associated on both legs

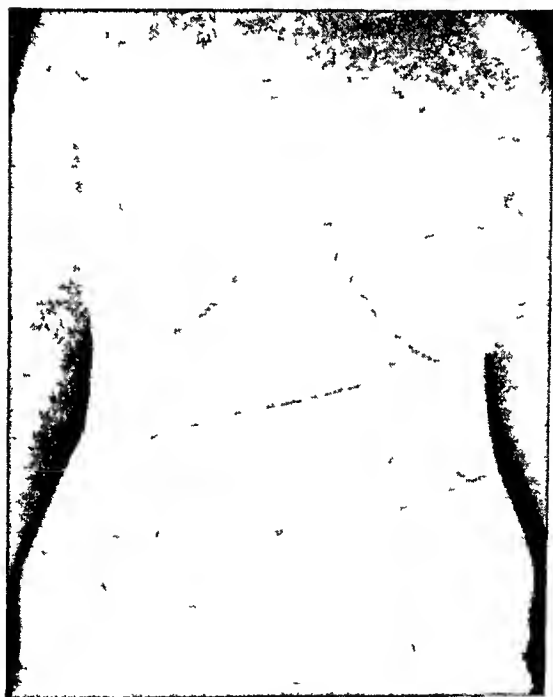


FIG 20 Case 16 Eruptive form (papulo-pustular form) of xanthoma on the front of the body with enlarged liver and spleen

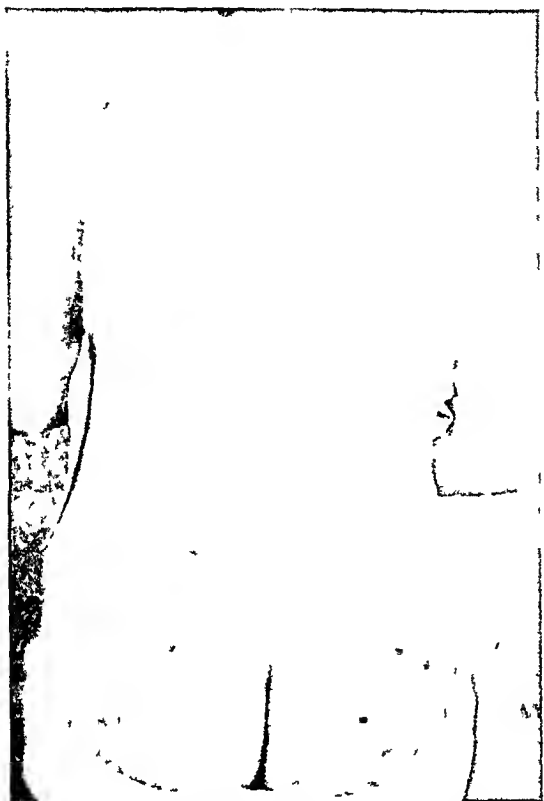


FIG 21 Case 16 Eruptive form of xanthoma (papulo-pustular form), on the back

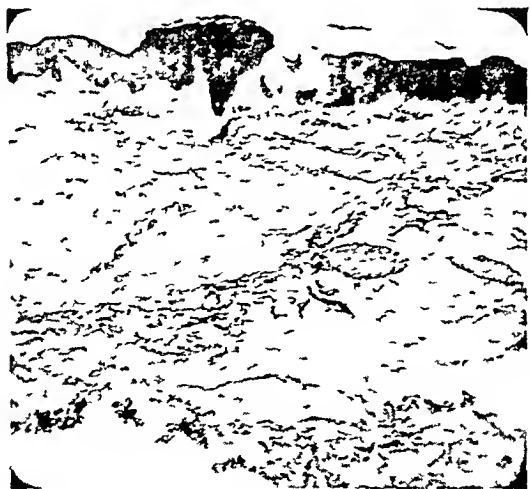


FIG 22 Case 16 Histological picture of the eruptive (papulo-pustular) form of xanthoma
Notice that no xanthoma cells are seen

fingers' breadth below the costal margin Both were firm, smooth, non-tender No signs of portal obstruction were visible, including the absence of esophageal varices

The urine contained constantly 0.5 per cent albumin, increased urobilinogen and urobilin, occasional granular casts and rare red blood cells Icteric index 14 on admission, a year later when the icterus had subsided it was 4.5 and the indirect Van den Bergh reaction less than 0.5 mg per cent Non-protein nitrogen 39.6 mg per cent Red cell fragility normal Basal metabolic rate varied between plus 25 and plus 35 Blood sedimentation rate 93 mm in 1 hour (Westergren) Blood cholesterol 570 mg per cent

A year later the patient was put on a cholesterol free diet, following which regime the itching disappeared and the skin lesions diminished, but they did not disappear completely Patient was given thyroid, gr 1 daily, in addition to the cholesterol-free diet Within the last year small xanthelasma lesions developed on both upper eyelids She had several furuncles which had to be treated surgically Albuminuria and moderate hypertension remained unchanged as did the enlargement of the liver and spleen

11/5/35	Serum total cholesterol	532 mg %
11/26/35	" "	606
	" free "	317
	" cholesterol esters	289

Cholesterol-free diet instituted

	12/3/35	12/11/35	12/18/35	1/8/36	1/29/36	6/24/36	9/4/36	11/20/36
Serum total cholesterol	521	360	329	346	372	300	435	400
free cholesterol	290	112	127	137	176	43	138	
esters cholesterol	231	248	202	209	196	257	297	
Total phospholipids						370		
Diaminophosphatide						228		
Monoaminophosphatide						142		

Discussion and Comment The first patient (Case 14) died from hepatic failure due to chronic biliary cirrhosis, having been severely jaundiced for four years The xanthelasma developed two years after the onset The eruptive papulo-pustular lesions came and went During these years a pulsating angiomatous xanthoma developed in a tendon of the left little finger

Necropsy showed a severe cirrhosis with fat-loaded reticulum cells and foam cells scattered through the liver There is no question that the hepatic cirrhosis did not result from alcoholism or chronic infection of the bile ducts, but from the formation of xanthomatous tissue which led to connective tissue and scar formation, as in Chvostek's case

The second patient, Case 15, 32 years of age, died from a coronary thrombosis having been jaundiced for five continuous years The course of the disease was exactly the same as in case 14 At first there was painless jaundice accompanied by enlargement of the liver and spleen In both instances operation was performed because of a diagnosis of cholelithiasis but stones were not found In the second case the surgeon noticed thickened bile ducts but no histological examination of the bile duct was

made Cutaneous tuberous and plain xanthomata developed in both about one year after the jaundice was first noticed It may be emphasized that chronic jaundice in the usual biliary cirrhosis is not accompanied by the formation of xanthomata even after a very long period of jaundice In cases of ordinary biliary cirrhosis the cholesterol in the serum may be high and in cases of biliary cirrhosis with partial obstruction it may be very high, but no xanthomata develop The appearance of xanthomata during a prolonged jaundice suggests a special type of hepatic cirrhosis and bile duct involvement These are histologically identical with xanthoma cell formation in the skin

The total cholesterol in the serum of both patients was high and the ratio of cholesterol to cholesterol esters was inverted We attribute this inversion to the severe damage of the hepatic tissue The phospholipids in the serum of both cases were not examined We would expect in such a severe liver disease, in the light of experience gained from the separate determination of diamminophosphatide (sphingomyelin) and monoaminophosphatide (lecithin-cephalin), a low normal sphingomyelin but high lecithin and cephalin values

A very intensive eruption of papulo-pustular xanthomata was seen in all of these three cases The eruptive form of xanthomata changes in degree during the disease, because this form depends, in our experience, to a great extent on the cholesteremia

The patient (Case 15), a young woman of 32 years, died of coronary thrombosis Although an autopsy was not done, it seems very likely that the coronary thrombosis in this case was due to the same etiology which caused the xanthomata of the skin, liver and bile duct Especially since we learned from the cases reported in the literature that juvenile patients who exhibited xanthomata of the skin and tendon sheaths died suddenly from heart disease and autopsy revealed severe xanthomata formation on the valves, large vessels and coronaries

The third reported patient (Case 16), is alive and under our observation She differs from the two other patients in two points First, she is not constantly jaundiced At times she has a slight yellowish tinge to the sclerae, sometimes a real jaundice, and other times, as at present no trace of jaundice Secondly, three years after the onset of symptoms, she had only small xanthomata of the skin of both eyelids However, the main symptoms in the three cases are chronic enlargement of the liver and spleen, constantly high cholesterol values in the serum, and independent of the jaundice, itching eruption of nodular pustular xanthomata

It is astonishing that this form of xanthomatous disease of skin and liver with xanthomatous cholangitis is almost unknown, because it is never considered in the modern textbooks on medicine Yet this peculiar complex of symptoms and its underlying pathology have been described by classical authors We find it stated in some articles that Rayer in 1835⁹⁷ de-

scribed "plaques jaunâtres des paupieres" and that Addison and Gull in 1850¹ named the same disease "vitiligoidea planum et tuberosum" But nowhere in the modern literature are Addison and Gull credited with the full description of the symptom complex of skin xanthomata with a peculiar form of cirrhosis of the liver although in fact these authors did describe three patients with jaundice, xanthomata of the skin and hepatic cirrhosis in Guy's Hospital Reports, 1850 From the same hospital, Fagge,³⁶ Howes,³⁶ Murchison⁷⁹ and Pye-Smith^{94, 95} report similar cases in the Transactions of the Pathological Society with detailed autopsy findings and histological examinations In the French literature Bazin,¹² Hillariet,¹² Chambard,¹² in 1878 report similar cases with xanthomata and jaundice Besnier¹⁶ in 1876 describes tuberous xanthomata and plaques with liver, heart and arterial disease

The clinical description of Addison and Gull in 1850¹ is so important that one of the reported cases may be quoted verbatim to demonstrate the similarity to one of our reported patients (Case 15)

"Case of Eliza Parachute, aged 33, of middle stature, moderately well nourished, mother of six children, catamenia regular Her present illness began in 1848, she attributes it to fright, and to a blow received in the left groin whilst attempting to separate two men who were fighting Two days after this she became jaundiced, and had from time to time severe paroxysmal pains about the hypochondria, lasting for a day or two, the liver being also enlarged and tender Four months after the commencement of the jaundice (August 4, 1848) she was admitted into the Hospital under the care of Dr Hughes She remained in until September 26, and left much in the same state she was in when admitted There was at this time nothing complained of beyond itching and irritation of the skin common in jaundice The present affection began after the jaundice had continued 14 months, when she again came under the care It first appeared in the hands, spreading across the flexures of the joints of the fingers and palms Soon afterwards a yellowish patch of discoloration began near the inner canthus of the eyelid, and then a precisely symmetrical one at the same part on the opposite eyelid These patches are very slightly raised, and not obviously indurated, they have extended very slowly At this time the patches on the face existed as above described Along the ridges bounding the flexures in the palm and about the joints of the fingers, there were yellowish, opaque, irregular, and somewhat raised lines About the thumb, first joints of the fingers, and inner interior parts of the wrists, there is a gradual transition to a tubercular prominence of the affected parts, and some distinct tubercles exist on the elbow and knee"

In the same paper Addison and Gull¹ gave the first description of the eruptive form of xanthomata diabeticorum in a diabetic patient, in a wonderfully picturesque manner The pupils of Addison at the Guy's Hospital report the first anatomical findings in the liver, bile ducts and arteries Moxen (Trans Path Soc, 1873)⁷⁸ reports the case of a man 32 years of age, severely jaundiced for two years with two attacks of colic, xanthelasma on the palms, scrotum, back, ears, cheeks and lids He died of hemorrhage from a hepatic lesion The postmortem examination showed only hepatic cirrhosis, no gall stones

"The gall ducts throughout the organ were excessively wide so that on section of the liver their contents welled up in enormous quantity, being a white clear fluid, in strong contrast with the serum of the blood which was golden yellow. These dilated gall ducts had xanthelasma looking patches within them—that is, white opaque patches. The hepatic duct at the point of union of its two divisions was swollen from the pressure in it of a firm, tough matter making a little soft knot of the size of an almond around it and in its walls. The microscope showed only fibrous scar tissue in the thickening."

This is like the operative finding in our Case 14. Similar reports are found in the literature (Futcher,⁴¹ Weidman¹⁵⁰). The scar tissue in all these cases, which almost completely occluded one of the bile ducts, is granulomatous in character resulting from xanthomata patches lining the wall of the bile duct. Xanthomatous patches were found on the arteries, especially the aorta, on the trachea near the bifurcation, and one in the capsule of the small spleen. Hilton Fagge³⁶ reported in the same volume of the Transactions (1873, v, 242) a case of vitiligo (which has since received from Erasmus Wilson the more euphonious title of xanthelasma) with a pathological report by Dr. Howse. The patient was jaundiced for seven years continuously. Xanthomatous patches were found on the eyelids, hands, abdomen, lips, larynx and trachea, hepatic cirrhosis, enlarged spleen with a large number of minute white grains within it. The lungs and brain were normal. The left auricle, aorta and pulmonary artery and almost all the vessels presented a large number of yellow spots and patches.

"They were sharply defined and raised slightly above the level of the lining membrane of the vessel." "The nature of the growth appears to be essentially the same wherever it occurs, whether in the mucous membrane, on the tendons or on the skin. It appears to be a kind of universal atheromatous change. From wherever the sections are taken they show fine granular cells variously disposed amongst the fibrous tissue of the part affected. In the other growths they undergo still further degenerative changes becoming converted into lumps of calcareous matter, crystalline bodies, etc. Thus it would be a matter of indifference whether we should speak of the cutaneous disease as an atheroma of the skin or of the arterial affection as a xanthelasma of the aorta."

A third case with autopsy was described by a third physician of Guy's Hospital, Pye-Smith, at the same time,⁹⁴ in the Transactions of the Pathological Society 1873, p. 250. A woman 49 years of age had attacks of colic over a period of two years with intermittent jaundice but her urine was always dark. She showed xanthelasma only on both eyelids. She died of an intercurrent severe erysipelas. The postmortem examination revealed only one calculus in the gall-bladder but the biliary ducts were found to be much dilated. "Patches precisely like those in the eyelids and hands were found on the surface of the spleen and in the mucous membrane of the dilated hepatic ducts." The liver showed a slight degree of interstitial cirrhosis. "The patches in the ducts looked just like atheroma in the artery with which condition indeed, they correspond histologically."

Already in 1882, 23 similar cases with jaundice and xanthelasma were

collected and described by an English Committee for investigation of xanthomata (J Hutchinson, A Sangster and H R Crocker⁵⁴) The question that xanthomata exist without liver disease was decided by the report of cases of xanthomata plana and tuberosa without jaundice In 1884, Balzer,¹⁰ referring to three patients with liver disease and xanthomata in the French literature, believed that he proved an infectious etiology of the disease but this was never confirmed In 1889 Hardaway⁴⁹ speaks of xanthomatous diathesis in a case to which we shall refer later He also suggested that xanthomata is a "diathesis" and that its connection with hepatic disarrangement was entirely secondary, or in other words, that jaundice occurring during the course of the disease was a consequence of a deposition of xanthomatous tubercles in the "liver" This wise conception was not accepted and P Weber in 1903¹⁴⁸ as well as Fitcher in 1905,⁴¹ reporting three cases from Osler's wards at Johns Hopkins, believed that chronic obstruction of the bile duct is the primary cause of the development of the xanthomata This opinion of Fitcher is surprising because he describes "that on section of the liver the bile ducts stood out everywhere looking like sclerotic arteries The walls of the bile ducts are considerably hypertrophied containing elastic fibers and the lumina are lined with a mass of lymphoid and planum cells similar to those already described in the skin lesion" Posner, in 1909,⁹² describes a patient with bile duct obstruction who was operated upon but no obstruction found Xanthomata of the skin developed after the operation Hepatic cirrhosis and all kinds of xanthomatous changes in the organs were found at autopsy In 1900 Chvostek⁸² pointed out that "jaundice and xanthelasma" are the result of the same disease, namely they are due to a xanthomatous involvement of the liver which results in cirrhosis of this organ and to a xanthomatous involvement of the skin which is evident as xanthelasma"

S C Dyke, 1928,⁸⁴ in his paper on "Hypercholesteremic Splenomegaly" deals with the same disease—jaundice, xanthelasma planum and tuberosum, xanthomatous involvement of spleen and lymph nodes Buerger²⁵ describes a female 55 years of age with extensive xanthomata tuberosa and plana, jaundice and hepatic cirrhosis with the extreme total cholesterol value of 2575 mg per cent, 1444 mg per cent free and 1131 mg per cent esters A similar case with 1020 mg per cent total cholesterol is described by Weidman and Boston¹⁵² The autopsy findings in these cases showed biliary cirrhosis, xanthomata cells on the splenic and hepatic capsules, also on a scar of herpes zoster (like Hardaway's case) besides the extensive tuberosus xanthomata of the skin The most important feature of this paper is not the occasional finding of a polyp of questionable adenocarcinoma of the ampulla of Vater, but the photograph of the histological picture of the wall of the gall-bladder and the similarity of findings on the wall of the bile duct, both showing extensive xanthomatous changes and xanthomatous scar tissue It was recognized that the common bile duct was enlarged to the size of an

average thumb and the head of the pancreas was indurated, however, a cause for the dilatation in the form of biliary obstruction could not be demonstrated (Finding on laparotomy, immediately after which the patient died)

THE ETIOLOGY OF THE BILIARY CIRRHOSIS FOUND IN CASES OF JAUNDICE AND XANTHELASMA

Chvostek ³² showed for the first time that xanthoma cells and xanthomatous scar tissue are found in these cirrhotic livers

Our Case 14 (already reported by Schilling) exhibited the same findings of xanthoma cells scattered throughout the liver as the case of Chvostek and the case reported by Weidman and Freeman in 1928 ¹⁴⁹ It is evident that these nests of xanthomatous cells resulting in xanthomatosis of the liver undergo destruction sooner or later The result is the development of connective scar tissue and cirrhotic changes of the liver However, this process in the xanthomatous liver is not necessarily the main cause of the large cirrhotic liver of the biliary type of cirrhosis in all the described cases The main clinical symptom of this disease, "jaundice of years duration," would not be explained by a simple cirrhotic process of the biliary type

On the basis of an intensive study of the literature, and our experience, we believe that the xanthomatous changes on the walls of the larger bile ducts which are observed in almost all reported autopsies, and which give rise to the thickening as well as to the partial obstruction and dilatation of the bile ducts through the formation of xanthomatous scar tissue, are the cause of this peculiar biliary cirrhosis We know that chronic inflammation of the bile ducts leads very often to biliary cirrhosis Hence it seems reasonable that degenerative changes in the wall of the bile ducts due to xanthomata formation may also produce cirrhotic livers

The name "xanthomatous biliary cirrhosis" with xanthomatosis of the bile ducts may therefore be ascribed to this form of cirrhosis In naming this form of cirrhosis, first described by Addison and Gull in 1850, we would like to say that xanthomatous biliary cirrhosis is only one of the features of a systemic and usually hereditary disease which may involve different organs and produce different clinical pictures We shall see later that there are two distinct groups of organs which may be affected by xanthomatous changes resulting in peculiar symptom complexes However, xanthomatous changes may be observed isolated in one organ and, as in a few cases, involving almost every organ The former conception that the cause of the development of xanthomata is due to biliary cirrhosis and jaundice resulting from obstruction of the common bile duct by stones, inflammatory changes or tumor, does not meet with the facts and our clinical experience

Xanthomatous biliary cirrhosis due to xanthomatous involvement of the bile ducts shows in some instances nests of xanthomatous cells in small

areas of the liver tissue itself and in the spleen described as saffron yellow spots of pinhead size. These little xanthomata in the liver and spleen as well as in the capsule of the liver and spleen do not result in those extensive cirrhotic changes above described as "xanthomatous biliary cirrhosis" although they may be found in the same livers together with the xanthomatous involvement of the bile ducts.

On the other hand, the development of larger areas of xanthoma cells in the liver and especially in the spleen is described without jaundice and without cirrhosis but with enlargement of liver and spleen. In these cases of hepatosplenomegaly a high grade of lipemia was primarily observed. In 1931 Buerger and Grutz^{23, 24} describe such a patient, a boy of eleven years of age with a large liver and spleen, 9476 mg per cent of fat, 686 mg per cent total cholesterol, 310 mg per cent free and 376 mg per cent ester cholesterol. This boy was not jaundiced but there were xanthomata on the face, neck, arms and buttocks, also xanthomata in the mucosa of the mouth and in the larynx. Buerger and Grutz^{23, 24} report that the skin manifestations, in contrast to the findings of xanthomata tuberosa, did not show true xanthomatous tissue but only a few xanthoma cells. We would suggest that these nodules belong to the eruptive group of nodular papular xanthomata which come and disappear as described in our Cases 14, 15, 16 and as in severe lipemia in the diabetic Cases 21 and 22. Buerger and Grutz have not published up to now the further development of histological lesions in this unusual case but we agree with them that this case is different from the cases with jaundice and xanthelasma due to "xanthomatous biliary cirrhosis". The anatomical findings in liver and spleen of the "hepatosplenomegalic type without jaundice" may be similar to the findings of Lubarsch⁶⁸ in 1918, and Bross²² in 1920 in a case of xanthomatosis and diabetes mellitus with high grade lipemia where the enlarged liver and spleen as well as all lymph glands were filled with xanthoma cells. The case of Lubarsch-Bross forms a transition to a group to be presented later as "secondary xanthomatous diseases" with xanthoma cell formation in spleen and liver in diabetic lipemia. This condition was first described by Schultze¹²¹ in 1912 as "lipoid cell hyperplasia of the spleen".

Chemical Findings In our three cases, as in all cases of xanthomatous biliary cirrhosis in the literature where cholesterol determinations were made, there is high total cholesterol and in advanced cases of cirrhosis an inversed ratio of cholesterol cholesterol esters. High total cholesterol is in conformity with biliary stasis while inverse cholesterol cholesterol ester ratio indicates severe liver damage according to Thannhauser and Schaber and many others. The bilirubin of the serum is high and shows a direct and indirect reaction because in this kind of cirrhosis as in other biliary cirrhoses, bile stasis and liver damage is the underlying pathological condition.

Only Case 16, the lightest case of the three reported, was examined by our method to determine the monoamino- and diaminophosphatides. As

in the cases of cirrhosis the total phospholipids are high, the determination of lecithin (monoaminophosphatide) and sphingomyelin (diaminophosphatide) shows that the increase of total phospholipids in the serum is due only to an increase of monoaminophosphatide while sphingomyelin (diaminophosphatide) is normal or even diminished, a characteristic finding for all xanthomatous tissue, while in Niemann-Pick's disease the diaminophosphatide (sphingomyelin) is found excessively increased

Diagnostic Considerations The outstanding triad of symptoms in xanthomatous biliary cirrhosis is (1) enlarged liver and spleen with jaundice of years duration, (2) skin manifestations exhibiting tuberos and plain xanthomata of the elbows, knees, extensor surfaces of the extremities and buttocks, (3) hypercholesteremia with an inverse ratio of cholesterol cholesterol esters. The jaundice may be intermittent in character as in Case 16, but the liver and spleen remain enlarged and hypercholesteremia is always found, even during the time the patient does not show distinct jaundice. The skin xanthomata usually develop after the jaundice but in rare cases of tendon sheath xanthomata the xanthomatous biliary cirrhosis may develop in a later period of life. (Case 1 shows an inverse ratio of cholesterol cholesterol esters.) On the other hand, the xanthomata may develop very late as in Case 16. We are inclined to believe that the eruptive form of xanthomata (papulo-pustular form) may have been present in other cases reported in the literature, but the connection with the disease (that is with the hypercholesteremia) was not recognized. We would like to emphasize that this extremely itchy eruptive form which comes and goes is an aid to the early recognition of the disease.

CORRELATED FEATURES OF XANTHOMATOSIS OF THE NORMO-CHOLESTEREMIC TYPE

It is important to point out that certain features of xanthomatosis are found together. They are (1) xanthomata tuberosa and plana of the skin, (2) tendon xanthomata, (3) xanthomata formation on the endocardium and on the intima of blood vessels, (4) xanthomatous biliary cirrhosis and xanthomata formation in the liver and spleen. This group of xanthomata exhibit hypercholesteremia, high monoaminophosphatides, and high fat in the serum as well as in the tissues. The second group of xanthomatous diseases exhibit on the skin, if there is any skin involvement, most peculiar and for this group, characteristic universal lesions which are in localization, color and size, entirely different from xanthomata tuberosa and plana. This kind of xanthomata disseminata is associated with diabetes insipidus, involvement of the brain and nerve tissue, bones, lungs and lymph nodes. In contrast to the former group normal cholesterol or high normal cholesterol in the serum is the rule in this group.

I am very much indebted to Dr P A O'Leary, Dr H Montgomery and Dr A E Osterberg, Mayo Clinic, Rochester, Minnesota, for the permission to use Case 17 and Case 18 for publication in this paper.

XANTHOMATA DISSEMINATA

Case 17 S S, a man, aged 42 (1932) first seen in June 1927, had noticed increased thirst and polyuria in November 1925. He would drink about 20 glasses of water during the day and would wake up at night because he was thirsty. He could not remember any illness or other incident which might have brought on the condition. About the same time he noticed yellowish-brown elevated areas on the skin of the antecubital fossae. It seems probable that the appearance of these lesions antedated the onset of the diabetes insipidus but that they were not striking enough to attract the patient's attention for some time. Similar soft tumor-like nodules presently appeared in both axillae and on the sides of the neck, and smaller, paler plaques under the eyes. At his first visit, general examination was essentially negative except for the lesions on the skin in the areas mentioned. He was found to be passing not more than 2000 c c of urine daily and his oral fluid intake was recorded as not more than 2200 c c. The specific gravity of the urine varied from 1.006 to 1.012. Roentgenograms of the sella turcica were negative. The blood sugar was 0.10 per cent, the basal metabolic rate was normal, plus 3 per cent. A biopsy made from one of the nodules in the axilla revealed the typical picture of xanthoma.

The patient returned to the Mayo Clinic in January 1932, showing marked increase in the number and extent of xanthomatous lesions as compared with the status shown by photographs taken at the time of his previous visit. The progression had been so gradual, however, that he could not say whether they were still increasing or were stationary. About two years before this last visit, xanthomatous nodules had appeared around the anus and had been excised because of itching. They had recurred in an area of larger radius, and the itching associated with them formed his chief complaint. His thirst and polyuria were of less degree, he thought, than on his former visit. He had tried hypodermic injections of solution of pituitary in 1927 and had found that they controlled his thirst, but he had not experienced sufficient discomfort to continue the use of the drug.

Examination disclosed large areas of soft, confluent bronze-colored nodules in each axilla (figure 23). There were smaller areas in each antecubital fossa, where the nodules were pinkish-brown, some of these tumors were slightly pedunculated and as large as 2 by 1 by 1 cm. There were numerous smaller flat nodules on the neck, face, groins, and sides of the abdomen. Around the anus for a radius of from 6 to 7 cm the skin appeared smooth, gray and thick, perhaps owing in part to previous excision of nodules, at the periphery of this area were soft, sessile, pinkish tumors like those in the hollows of the elbows. A continuous ridge of nodules ran along the median raphe to the scrotum, where it ended in several nodular enlargements. Again, it was interesting to note that there were no lesions on the elbows, knees or surfaces subject to trauma. In the mucous membrane of the mouth there appeared five yellowish areas, one on the left margin of the tongue, one in each cheek, one in the left lower jaw and one in the uvula. There was no involvement of the posterior pharyngeal wall or scarring, as was present in Case 1. There were eight areas visible in the larynx and upper part of the trachea where the mucous membrane was similarly involved. As far as one could see down the trachea, the same condition was present. There was no scarring in the larynx or trachea and no embarrassment of respiration. On the upper part of each cornea covering the upper margin of the iris, was a yellow, slightly elevated mass resembling so closely some of the other nodules, particularly those in the mouth, that there seemed no reasonable doubt of their identical nature. Biopsy was made from a nodule on the arm and again revealed typical xanthoma, not differing essentially from the picture seen five years before in tissue from the same patient nor from that seen in sections made from the first patient (Case 1).

General examination was essentially negative except for the lesions described. The output of urine was between two and three liters daily, the specific gravity was

1010, urinalysis was negative. The concentration of hemoglobin was 10.8 gm (64 per cent), erythrocytes numbered 3.5 million per cu mm and leukocytes 11,700. Serologic tests for syphilis were negative. Roentgenograms of the thorax and sella turcica were negative. The eyegrounds were essentially normal. Analysis of the



FIG 23 Case 17 Xanthomata disseminata

chemical constituents of the blood gave these figures: cholesterol 167 mg, cholesterol esters 119 mg, total phospholipids 246 mg, fats as fatty acids 273 mg. One nodule was excised and the analysis of the dry tissue as follows: total cholesterol 4.55 mg per cent, cholesterol esters 3.66 mg per cent, fatty acids 3.64 per cent.

Treatment was begun as in the other case. Roentgen-ray exposures were made over the region of the sella turcica, both sides of the neck, and over the right arm. A diet low in calories and low in fat was tried. There was no improvement during the period that the patient remained under observation.

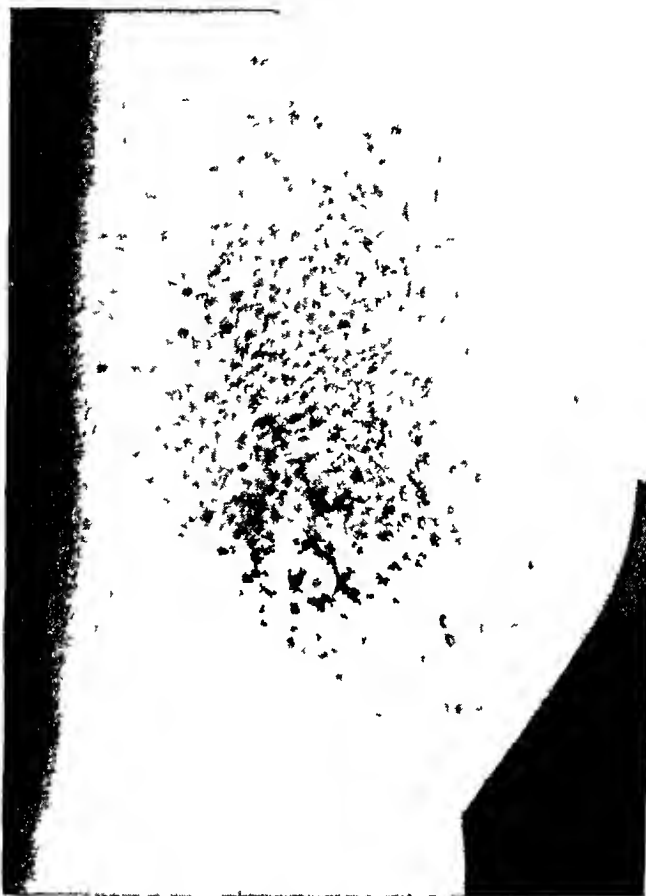


FIG 24 Case 18 Xanthomata disseminata in the axilla

Case 18 Mrs H A, married, aged 48 years, was examined at the Mayo Clinic in June 1936, because of polydipsia. In June 1935, she noticed small red and yellow lumps under the arms (figure 24) and in the groin which increased in spite of roentgen-ray treatment. In March 1936, many lesions developed on the eyelids (figure 25). Six months after the first onset of the cutaneous lesions (January 1936), she developed symptoms of diabetes insipidus, including marked polyuria and an



FIG 25 Case 18 Xanthomata disseminata of the eyelids

output of eight gallons of urine daily Diabetes insipidus was controlled fairly well by the use of pituitrin and amidopyrin Examination of the skin revealed red-brown nodules from the size of a pea to a pin, but none on the elbows, buttocks, knees and fingers There were also lesions in the mouth Blood chemical studies were as follows

Date	6/26/36	7/9/36
Total cholesterol	214 mg per 100 c c	235 mg per 100 c c plasma
Total fat as fatty acids	302	250
Total phospholipids	305	269

The hemoglobin was 15.4 grams per 100 c c of blood, the erythrocytes numbered 4.9 million per cu mm and the leukocytes numbered 10,600 The differential count was as follows lymphocytes 31.0, monocytes 4.5, neutrophils 60.5, eosinophils 2.5, and basophils 1.5 per cent The flocculation test for syphilis was negative The urine showed specific gravity of 1.009 Roentgen-ray of the chest was negative Roentgen-ray of the skull, including the sella, showed a benign frontal hyperostosis

In February 1937, the patient returned The skin lesions had become much more numerous in the axilla and groin, and there was marked, diffuse, reddish infiltration of the face over the area usually involved by rosacea, made up entirely of milium xanthomata There was involvement under the eyes, over the axillae, lower portions of the breast, abdomen, labia, and inner surfaces of the thighs, and a few lesions were present in the cubital fossae,—all this in spite of the fact that the diabetes insipidus appeared to be quite well controlled (The liver was down about four fingers The spleen was not palpable) The patient was put on a low-cholesterol animal-fat-free diet The chemical analyses of the blood were as follows

Date	2/6/37	3/7/37
Total phospholipids	349 mg per 100 c c	297 mg per 100 c c plasma
Total cholesterol	273	231
Fat as fatty acids	514	405

At this time the erythrocytes were 4.6 million per cu mm and the leukocytes 8700 The urine showed a specific gravity of 1.007 There were xanthomata involving both cheeks, and the floor of the mouth There were some suspicious areas on the margins of the tongue, both arytenoid regions showed definite yellowish nodular areas

When the patient was examined May 10, 1937, she had been feeling well, and had been having very little trouble with thirst or polyuria She had been taking three amidopyrine tablets at night and three injections of pituitrin a week All the skin lesions were somewhat more extensive than in February The blood analyses on May 12, 1937, were as follows

Total phospholipids	260 mg per 100 c c plasma
Total cholesterol	208
Cholesterol esters	134
Free cholesterol	74
Total fat as fatty acids	290

The bilirubin was 1.0 mg per cent—reaction indirect (The liver was no longer palpable)

Comment and Discussion It is remarkable that this form of xanthomata, until the paper by Polano⁸¹ (1936) and Montgomery⁷⁶ (1937) appeared, was confused with the other manifestations of xanthomata, although it differs in appearance, color, localization and size from the tuberous and flat form of skin xanthomata Under the title "xanthoma multiplex molluscum lipoides" Virchow,¹⁴⁵ who was the first to describe xanthoma

disseminata, adds to his paper a colored lithograph. On this lithograph the characteristics of this kind of xanthomata can be seen. The localization is on the hollow of the knees and elbows, not on the extensor surface, the color is not ochre or carrot-like but the color of a lemon at first and later dark brown like mahogany, sometimes with a metallic shiny surface. Virchow's patient was first seen by the famous ophthalmologist, von Graefe, because he had a xanthomatous nodule on the cornea similar to other cases of xanthoma disseminatum described in the literature by Weidman and Freeman,¹⁴⁹ and our Case 17. Stephen MacKenzie⁹⁸ in 1882 described, under the title, "Two Cases of Congenital Xanthelasma," two brothers and one sister with this peculiar kind of skin xanthomata (disseminata) in such an expressive manner that the difference between other xanthomata of the skin is seen at once. We quote his original description verbatim.

"Samuel H., aged 45. The eruption consists of very slightly raised, soft smooth patches of a lemon or chamois leather color, arranged somewhat in ridges or lines. The patches are of irregular shape and size, none much larger than a pea, and some not much larger than a pin-head. In places, as in the neck and abdomen they are so closely packed together as to appear confluent, but on stretching the skin the patches are separated by furrows. The larger patches are of deeper color and well defined, but the smallest are of a very faint lemon tint, fading into the healthy skin. The color is deeper in the exposed parts (as in the neck) than in covered parts. The affected skin is elastic and pliable and can be readily pinched between the fingers. There is not and never has been any itching of the skin and the patient has never experienced any inconvenience from it.

"*Distribution.* None on eyelids (most of the patients show affection of this part) nor on any part of the face or scalp. The neck is markedly affected, a band of the yellow plaques extending round it like a collar. From the neck the eruption extends over the scapulae and clavicles slightly. Both axillae are affected and the patches extend down over the integument covering the coracobrachialis and the biceps muscles. The bend of each elbow is slightly affected. There are a few faintly marked patches in the skin over the lower margins of each pectoral muscle. The lower lateral parts of the abdomen, the pubes, base of penis and scrotum are slightly and the groins are markedly affected. In the popliteal spaces are quite well marked patches.

"His brother, Jonathan H., aged 47, and his sister present a condition of the skin identical in character with that described on the neck, axillae, bend of elbows, groins and popliteal spaces. The sister is older than her brothers and remembers the eruption on the brothers' and on her own skin as babies. They have never caused any disturbance of their health. Neither has suffered from jaundice. Their paternal grandfather had a similar affection of the skin."

The familial occurrence of tendon xanthomata is widely known, the familial occurrence of xanthomata disseminata is only described in these cases of MacKenzie.

In studying the literature, we found xanthomata disseminata described but not differentiated from other xanthomatous manifestations, by Virchow¹⁴⁵ (1871), Poensgen⁹⁰ (1883), Eichhoff³⁵ (1884), Koebner⁶¹ (1888), Tschistakow¹⁴⁰ (1891), Anderson² (1882), E. Rhodes⁹⁸ (1906). In an outstanding but not commonly known paper Pusey and Johnstone⁹³ (1908) describe an 18 year old boy with a xanthomatous skin lesion "of

the diabetic type," associated with diabetes insipidus. The patient voided five liters of urine daily, specific gravity 1 002 to 1 006. The xanthomata are easily recognized by their description and localization as xanthomata disseminata. The skin was covered with an eruption varying from the size of a pin-head to a millet seed. The color was reddish in the small papules to a glistening yellow or bronze in the larger ones, which were confluent. The nodules were also seen on the mucosa of the mouth, epiglottis and larynx, cornea and sclera. The patient had spells of dizziness and fainting, during which he asked for water. Two years later tracheotomy was performed in order to relieve laryngeal stenosis caused by xanthomata. Later the spells of dizziness disappeared, but the diabetes insipidus persisted. Pusey deserves credit for having first described the clinical syndrome consisting of a peculiar form of skin xanthomata "intermediate form clinically between xanthoma diabeticorum and xanthoma multiplex" and diabetes insipidus. This peculiar form is, however, xanthoma disseminata and diabetes insipidus. He did not report in his first communication⁹³ (1908), as is erroneously quoted, xanthomata of the skull. W. H. Siemens¹²² describes, under the heading of xanthoma multiplex, what we believe to be xanthoma disseminata. Siemens, in collaboration with Rosenthal and Breunisch^{99b} first recognized that there are xanthomatous skin manifestations which are associated with normal cholesterol values in the blood in contrast to xanthomata tuberosa and plana. The difference in the appearance and the type of xanthomata was not emphasized by the various authors because the histological findings were the same as in xanthomata tuberosa and plana, and also because no single man observed a sufficient number of cases. Spillman and Watrin¹²⁶ (1921) describe in the French literature a boy who had xanthomata disseminata (according to the published photograph and to the description and the localization of the skin lesion) and diabetes insipidus. Neither bone changes nor exophthalmus were found. Turner, Davidson, and White¹⁴¹ (1925) indeed were the first who differentiated xanthomata disseminata from other xanthomatous eruptions. They reported and photographed a patient, who exhibited this characteristic kind of xanthomata. They describe the papules as 1 to 4 mm in diameter, varying in color from golden yellow to chocolate brown, distributed all over the body, around the neck, axillae, down the arms, involving both flexor and extensor aspects, eyes, abdomen, epiglottis, lateral aspects of the thighs and buttocks. The lesions of the mouth, pharynx, glottis, epiglottis, larynx and bronchi, as shown in the pictures, are unique in their extensiveness. The patient had an inspiratory and expiratory wheeze and the stenosis was so threatening that a tracheotomy had to be made as in Pusey's case.*

* Urbach (1928)¹⁴² describes a new manifestation of xanthomatosis with the name "lipoid proteinosis." The chief clinical manifestation is severe hoarseness. In the developed disease all cases present fairly hard, yellowish-white infiltrations of the inner surface of the lips, soft palate, fauces, uvula or under surface of the tongue. There are also some scar-like depressions. The larynx is similarly and severely involved. Two forms of the lesions are distinguished: (1) nodular and (2) hyperkeratotic lesions.

The clinical identity of these cases with those of Pusey and Johnstone, 1908,⁹³ Turner,

This patient, like Pusey's, had diabetes insipidus for three years, the onset of which coincided with that of the skin manifestations. Death occurred. The postmortem findings were very important because they showed for the first time that xanthomatous tissue may develop in the lung and pleura and produce a severe fibrosis of the lung. Roentgen-rays of the lungs were not taken, so that the very impressive picture of diffuse little nodules simulating miliary tuberculosis, but consisting of xanthomatous tissue, was missed during life. It is very important to note that the autopsy which showed xanthomatous plaques on the mucosa of the stomach did not show any involvement of the liver, of the vessels, or of the heart. The examination of the brain showed conglomerate xanthomata cells in the pituitary and the tuber cinereum. Unfortunately the bones were not examined. Pusey and Johnstone's⁹³ patient and that of Turner, Davidson and White¹⁴¹ were the first in whom the triad (1) xanthomata disseminata, (2) diabetes insipidus (brain involvement) and (3) xanthomatous disease of the pulmonary tissue was observed. Involvement of the bones has not been found, probably this was not looked for. In both cases there were neither xanthomata plana nor tendon sheath xanthomata, nor involvement of the blood vessels, bile ducts or liver. Blood sterols were normal in contrast to the reported cases in the other groups of xanthomata.

Recently Horsfall and Smith (1935)⁵³ reported under the title, "Lipoid Granulomatosis, Defects in the Bones, Exophthalmos and Diabetes Insipidus," a case with the complete clinical symptom complex of the group of xanthomatous diseases with normal cholesterol. The patient exhibited, according to the published photographs, typical xanthomata disseminata all over the body. The autopsy showed xanthomatous involvement of bones, lungs, dura of the brain, pituitary and spinal cord, lymph glands and spleen. Tendons, liver, bile ducts, and vessels were free, and xanthomata of the tuberous or flat form were not found. The cholesterol of the blood was normal.

K. Hoefer⁵² describes a seven year old boy with xanthomata disseminata. In this case xanthomata disseminata were combined with diabetes insipidus but this patient had in addition to these symptoms, exophthalmos and characteristic skull defects as described by Hand, Schueller and Christian.

Hermann and Nathan⁵⁰ describe a patient with xanthomata disseminata and normal cholesterol in the blood. The lungs and bones were not examined. Diabetes insipidus was not present.

In 1931 Finney³⁷ reported a case of typical xanthomata disseminata.

Davidson and White, 1925,¹⁴¹ and Finney, 1931,^{37, 38} is obvious. The photographs and colored pictures of the mouth and larynx published by Urbach are completely like the pictures of the case of Turner, Davidson and White. The skin manifestations of the "lipoid proteinosis" described by Urbach,¹⁴⁴ simultaneously with the lesions of mouth and larynx, are characterized by numerous pinhead-sized lesions grouped in mulberry-like, warty clusters. These lesions are, in view of size, appearance, localization and color (brown-violet sepia) identical with the lesions described first by Virchow 1871,¹⁴⁵ MacKenzie 1882,⁶⁸ and by different authors and are classified according to Polano,⁵¹ Montgomery and Osterberg⁷⁶ as "xanthomata disseminata."

situated on the eyelids, neck, axillae, groin and scrotum, some of the tumors were pedunculated (described as molluscum by Virchow) The mucous membranes of the mouth and larynx were involved The scarring of the larynx was "rhinoscleroma-like" The histological characteristics of these small xanthomata were the same as are seen in xanthomata plana and tuberosa xanthoma cells, chronic inflammatory and scar tissue This patient developed, one year after the onset of xanthomata disseminata, symptoms of diabetes insipidus with a daily urine output of six liters The cases of Finney, Montgomery and New,³⁸ Weidman and Schaffer,¹⁵¹ Montgomery and Osterberg,⁷⁶ show that diabetes insipidus and xanthomata disseminata may occur without bone and lung involvement The case of Weidman and Schaffer showed as a peculiar feature in the postmortem examination a xanthomatous involvement of the pons, this was also found in the case of Chiari^{29, 30} The involvement of the brain is not confined to the pituitary or the tuber cinereum as found in the patient presented by Weidman and Freeman¹⁴⁹ We shall discuss this later under a third group of patients

It is evident that we have to deal with two clinical symptom complexes of xanthomatous diseases These are to be distinguished by the kind of xanthomata exhibited on the skin, the organs involved and by the cholesterol figures found in the serum The one group consists of cases showing xanthomata tuberosa and plana, tendon sheath xanthomata, xanthomatous biliary cirrhosis with xanthomatosis of the bile ducts The other group shows disseminate xanthomata on the skin, xanthomatous involvement of the bones, skull, dura, brain (diabetes insipidus), scattered nests of xanthomata cells in the liver, spleen and lymph nodes without jaundice, but neither xanthomatosis of the bile ducts with xanthomatous biliary cirrhosis nor involvement of the tendons, intima of blood vessels or endocardium The kind of xanthomatous skin manifestations permits us to predict which visceral organs may be involved at the same time For this reason it is highly important to distinguish xanthomata disseminata from xanthomata tuberosa and plana as well as from the papulo-pustular eruptive form Even in the painstaking paper of Rowland^{100, 101, 102} we find his description of xanthoma disseminata mixed up with the description of the papulo-pustular eruptive form which may be present in hypercholesteremic conditions (diabetes mellitus and xanthomatous biliary cirrhosis)

Returning to Cases 17 and 18, it is evident that both belong to the second group of xanthomatous diseases (with normal cholesterol) Xanthomata disseminata and diabetes insipidus were the only features of this group observed in these cases According to our discussion of the literature, the xanthomatous manifestations in this group may be limited to these two symptoms, or they may involve other parts of the brain, the bones and the lungs

Histological findings In the photomicrograph of Case 17, larger groups of xanthoma cells are seen directly under the epidermis (figure 26) In

other xanthomata of the disseminata type the number of xanthoma cells is smaller, in older nodules xanthoma cells are not found at all

Chemical findings (Cases 17 and 18) The cholesterol content of the blood in these patients was a high normal, in fact in Case 18 the first de-

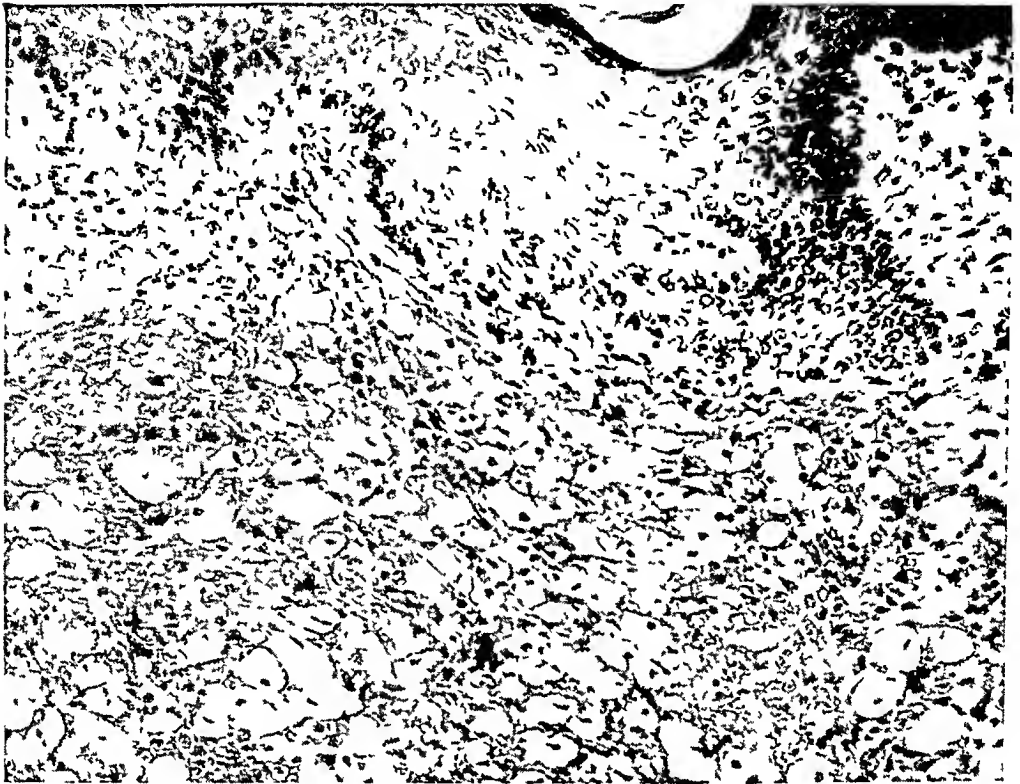


FIG 26 Case 17 Histological picture of xanthomata disseminata

termination was slightly increased but not as high as in the group of cases with xanthomata tuberosa and plana. In these cases only the total phospholipids were examined and not differentiated as monoaminophosphatides and diaminophosphatides. The low value of total phospholipids in Case 18 demonstrates also that this case belongs to the group of the normocholesteremic type. An organ analysis was not done because of the small size of the individual lesions. The significance of a normal content of cholesterol and phospholipids in the blood for the mechanism of the disease will be discussed later. At this point, however, we should like to emphasize that we do not believe that the two groups are different diseases although they are clinically different in regard to the organs involved and chemically different in regard to the cholesterol-phospholipid content of the serum. The two groups represent different features depending on the organs involved, but the anatomical changes characterized by xanthoma cell formation are the same.

OSSEOUS XANTHOMATA

Case 19 C S, a 51-year-old Italian carpenter, noticed multiple excrescences developing in the region of his right ear and at the external canthus of his right eye when he was 35 years old. There was sero-hemorrhagic discharge from the right and several years later from the left ear as well. At the age of 41 numerous soft

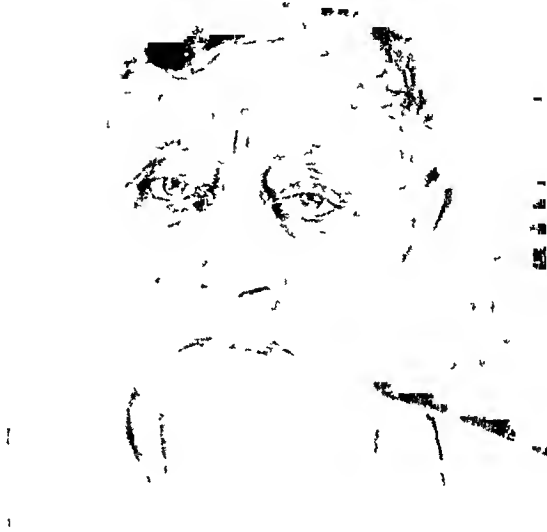


FIG 27 Case 19 Deformity of the skull and of the orbits

tender masses appeared on his head and drained sero-hemorrhagic fluid. Some of the older lesions ceased draining subsequently but other new ones appeared and drained. At about that time bilateral exophthalmos appeared and he began to suffer from polydipsia and polyuria (figures 27, 28). He was told at a hospital that his skull was paper-thin and that he had but three or four months more to live. He continued working, however, until at the age of 47 he fell down stairs and fractured his left femur and right humerus. In the Beth Israel Hospital, Boston, a plaster cast was applied and he was treated with irradiation by roentgen-rays. His fractures healed, the draining of the sinuses of his skull ceased and he was up and about, feeling well. His diabetes insipidus responded to a preparation of pitressin in oil. Fasting blood sugars were frequently elevated and a glucose tolerance test showed a diabetic type of curve. At no time was sugar present in his urine. His blood cholesterol values varied from 145 mg per cent to 235 mg per cent during his stay in the Beth Israel Hospital.

During the following years he developed a gradual unrecognized distention of the urinary bladder and became totally deaf. He knew of no member of his family with a similar condition or other manifestation of xanthomatosis.

We are indebted to Dr J D Adams for referring this patient to us and to Dr M J Schlesinger for permission to publish the histological slides.

On admission to the Diagnostic Hospital of the New England Medical Center January 9, 1937, he was slightly obese, not icteric, very thirsty and urinating at frequent intervals. His skull was strikingly deformed, showing a number of bulging areas and depressions which involved also the facial part of the head. The depressions were hole-like and funnel shaped, the surrounding bone was not thin, flexible or tender. None of these areas showed secretion. There was marked exophthalmos of both eyes. In the skin of both upper and lower lids, were several soft swellings, lighter and flatter than the xanthelasma (figure 29). His pupils were round, reacting to light and on accommodation, his fundi showed no abnormalities. Both ear canals



FIG 28 Case 19 Exophthalmos

were filled with soft, yellowish material which revealed no cholesterol crystals on microscopic examination. There was total nerve deafness. The mucous membranes of the mouth and throat showed no abnormalities. Heart and lungs were essentially normal. Blood pressure 160 systolic and 98 diastolic. In the lower abdomen the distended bladder extended above the umbilicus. After removal of 1000 c c of urine the bladder was still palpable above the symphysis. Liver and spleen were not palpable and not definitely enlarged on percussion. The right humerus and left femur were markedly deformed and shortened with limited motion in the right elbow and left knee joint. The skin of both hands was dry and hyperkeratotic. This condition was more marked over both lower legs where there were large, grayish-brown scales and onychogryphosis of the nails of both big toes. The thoracic spine was kyphotic and the patient's gait awkward, stiff and limping. He could walk only with the aid of a cane. No definite abnormalities of the central nervous system were demonstrated except the bilateral deafness, an occasional coarse tremor of the head and the *ischuria paradoxa*.

The volume of the urine varied from 4000 to 9600 c c daily. It contained from 36 to 75 grams of sugar daily. On a diet of carbohydrate 150 grams protein 80 grams, and fat 100 grams, with 20 units of insulin twice daily, he remained sugar-

free Under insulin treatment the urine volume diminished to between 1200 and 2500 c c daily

Fasting blood sugar varied from 224 to 252 mg per cent The glucose tolerance curve was diabetic in type



FIG 29 Case 19 Xanthomata protruding from both orbits

Serum calcium	10.5 mg %
" phosphorus	4.3 mg %
Icteric index	10

Phosphatase, 2.75 units in 100 c c serum

1/11/37	Serum total cholesterol	195 mg %
	" free "	67
	" cholesterol esters	128
2/3/37	" total cholesterol	200 mg %
	" free "	56
	" cholesterol esters	144

Basal metabolic rate minus 1 per cent

Roentgen-rays of the skull (figure 30) showed what has been described as a geographical map, the tables of the skull being irregularly eroded in areas varying from pin-point size to large irregular-shaped defects. The sella turca was not particularly enlarged. There was extreme increase in density at the base of the skull involving both mastoids, sphenoids and roofs of the orbits (figures 31, 32).

Roentgen-rays of the femora showed a few areas of decreased density in the head of the right femur, a large callous mass in the upper half of the left femur. There was a definite erosive lesion at the outer circumference of the right ilium, just above the head of the femur.

Chemical findings of Case 19 The cholesterol figures in this case show normal total cholesterol and normal cholesterol esters ratio in conformity with the figures reported in similar cases in the literature. In contrast to the normal cholesterol the total phospholipids are high. The individual determination of mono- and diaminophosphatides reveals that the increase of phospholipids is due to an increase of lecithin-cephalin fraction. The diaminophosphatides are low so that the ratio of diamino monoaminophosphatides which usually varies from 1.05 to 1.1 reads 1.66. We found a similar abnormal ratio in another one of this group but we would not like to stress this finding at this time because the significance of low values of diaminophosphatides which led to this abnormal ratio is not known.



FIG 30 Case 19 Skull roentgen-ray Geographic skull



FIG 31 Case 19 Roentgen-ray of the humerus, showing spontaneous fracture and xanthomatous cysts



FIG 32 Case 19 Roentgen-ray of the femur, showing spontaneous fractures and xanthomatous cysts

Histological findings of Case 19 The xanthomatous tissues of the excised nodules of the dura contained more granulomatous tissue than do tuberous xanthomata of the skin. There were scattered xanthoma cells and conglomerate nests of cells in granulomatous tissue as shown in the photographs (figures 33, 34). Giant cells and

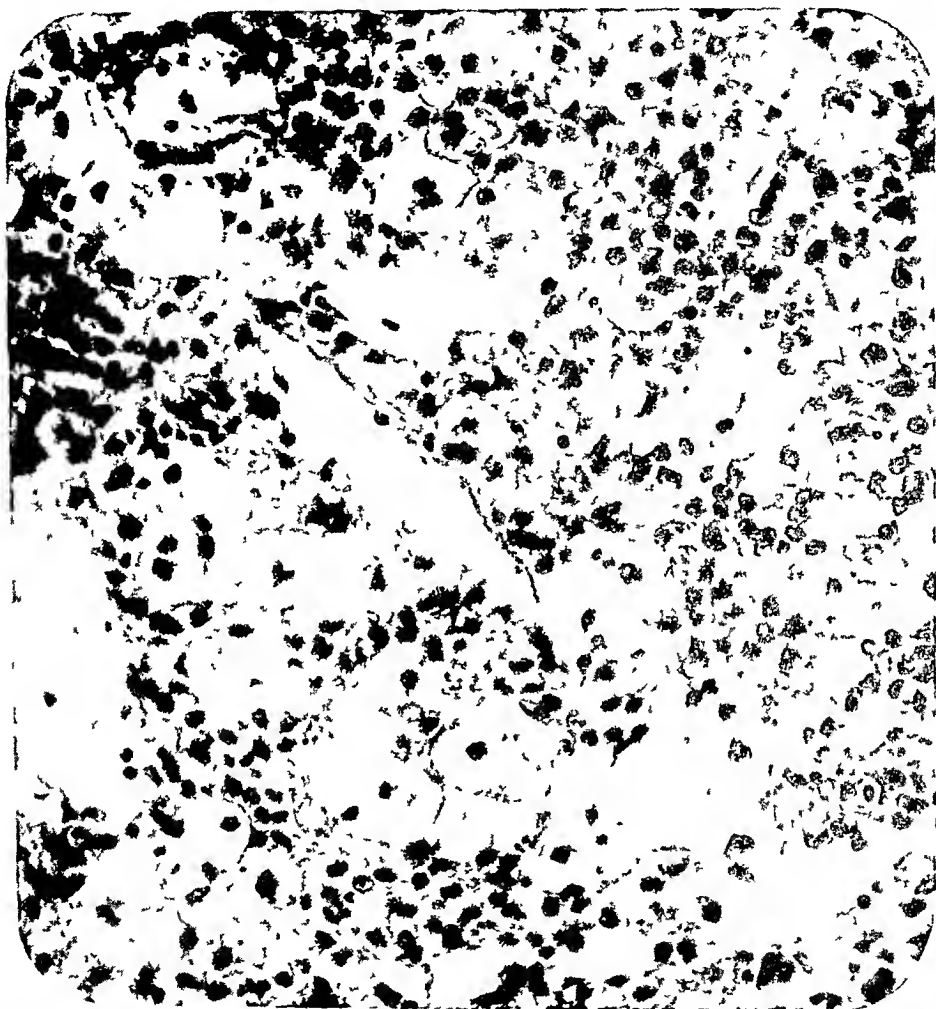


FIG 33 Case 19 Histological picture showing the xanthoma cells of a xanthomatous nodule of the dura

exudate cells were observed in the granulomatous nodules. There was no outstanding difference in the histological findings between the xanthomatous nodule of the dura and other xanthomatous tissue.

Comment and Discussion There is no question but that this case belongs to the group of cases which were first described by Hand (1893),⁴⁷ Kay (1905),⁵⁸ Dietrich (1913),³³ Schueller (1915),¹¹⁹ Christian (1919)³¹ under different headings of bone diseases associated with diabetes insipidus. These authors did not recognize that this group of patients belongs to the group of xanthomatous diseases although Dietrich³³ called his case "fibro-

xanthoma" Rowland (1928)¹⁰¹ deserves the credit of having proved conclusively (after reporting two of his own cases and discussing the others) that the defects in the membranous bones, the diabetes insipidus and the exophthalmos were due to xanthomatous changes in the bone marrow, to xanthomatous nodules of the dura and periosteum of the skull and orbit and to xanthomatous changes in the brain. The autopsy on one of Row-

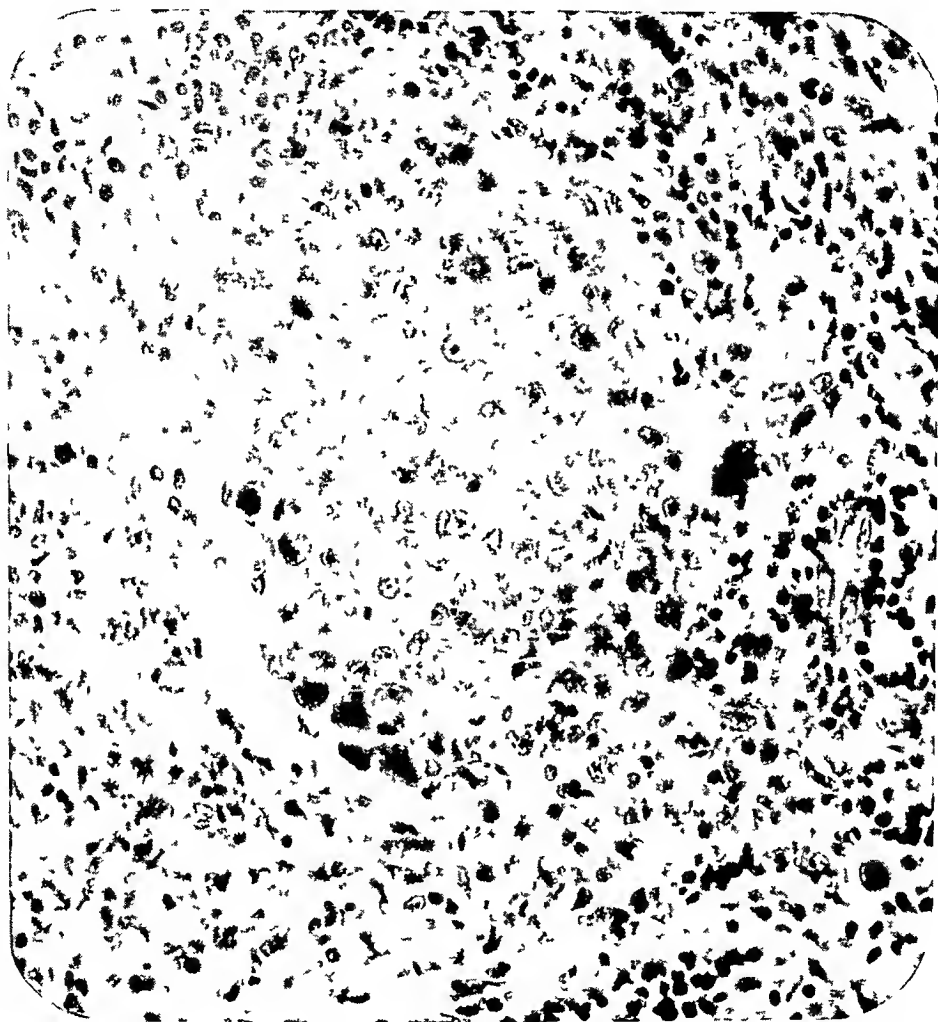


FIG 34 Case 19 A nest of xanthoma cells in a xanthomatous nodule of the dura

land's patients revealed these facts and showed that in addition to the bones, dura and brain, xanthomatous changes occurred in the lungs, pleura, lymph nodes and spleen.

We have reported above two cases (17 and 18) of xanthomata disseminata associated with diabetes insipidus. Similar cases in the literature show conclusively that xanthomata disseminata of the skin, xanthomatous changes in the brain (diabetes insipidus), xanthomatosis of the lungs,

lymph glands, spleen and bones belong to one group of xanthomatous disease (To this group belong the cases of Pusey and Johnstone,⁹³ Spillman and Watrin,¹²⁶ Turner, Davidson and White,¹⁴¹ Horsfall and Smith,⁵³ and K. Hoefer⁵²)

The question arises as to whether the Hand-Schueller-Christian symptom complex is a special kind of xanthomatous disease or whether it should be included in the group of xanthomatous diseases characterized above as involving the skin (by xanthoma disseminata), the bones, the brain and dura, lungs, lymph nodes, and the spleen. It would appear that Hand-Schueller-Christian's disease clinically belongs to this group and is not an independent clinical entity. To justify this assumption we offer the following facts: (1) We find xanthomata disseminata occurring alone, with diabetes insipidus, with the Hand-Schueller-Christian syndrome, and with bone lesions (Hand,⁴⁷ Horsfall and Smith,⁵³ Pusey and Johnstone⁹³), (2) xanthomata of the lungs occur with xanthomata disseminata, with bone lesions, with diabetes insipidus, and with Hand-Schueller-Christian syndrome (Turner, Davidson and White,¹⁴¹ Rowland^{101, 102}), (3) xanthomata disseminata alone or combined with diabetes insipidus, as well as the Hand-Schueller-Christian syndrome have a normal or high normal serum cholesterol.

The features of the Hand-Schueller-Christian syndrome which seem to separate it from the group are the lesions of the membranous bones and exophthalmos. The membranous bone lesions may occur, however, as a part of general osseous xanthoma without diabetes insipidus and without exophthalmos. Two cases of Fraser,⁴⁰ and our Case 20 (see below) illustrate this. The bone lesions as well as the exophthalmos have been shown by Rowland¹⁰¹ and others, to be due to granuloma-like deposits of xanthomatous tissue formed by the same components as other xanthomata, namely, xanthoma cells, giant cells, exudate cells and granulomatous tissue. Exophthalmos and skull lesions are therefore the result of the same underlying anatomical substrate, as are all xanthomatous diseases. Rowland (1928)¹⁰¹ collected 14 cases, Sossman (1932)¹²⁵ 45 cases (6 of his own) and Horsfall and Smith,⁵³ 50 cases of xanthomatous bone disease of the Hand-Schueller-Christian type. The number of cases would be decidedly higher if to these cases were added the patients with bone lesions and xanthomata disseminata with and without diabetes insipidus which belong to the same group.

The clinical features of our Case 19 do not differ essentially from the usual juvenile cases of the disease. The onset of the disease in this case at the age of 35 is, however, quite unusual, though there are already three cases of Hand-Schueller-Christian syndrome reported in patients over 40 years of age (Sossman,¹²⁵ Chester²⁸). The usual age of onset in these patients is the first decade of life. The draining ear of our patient was due to xanthomatous involvement of the mastoid bone as is also observed in

juvenile cases The enlargement of the bladder is probably due to failure of neurogenic control The patient exhibited the symptoms of *ischuria paradoxa* I had the opportunity to see another case of Hand-Schueller-Christian's syndrome with Dr Blackfan of the Children's Hospital in Boston This case, which is published by Dr Sossman¹⁻³ as Case 3 in his series has also at present a distended bladder and symptoms of *ischuria paradoxa* Disturbances of the bladder regulation are not reported in cases of diabetes insipidus It seems likely that xanthomatous changes in the spinal cord may be present

Case 20 S S, a four-year-old female child No family history of bone diseases She began to limp and roentgen-rays were taken by her physician which revealed multiple bone lesions of the hyperparathyroid type The child was sent to Dr Fuller Albright at the Massachusetts General Hospital to whom I am indebted for the privilege of seeing the child with him and for permission to use the case for this paper Her appearance was that of a normal four year old child There were no signs of xanthomatosis of the skin, skull formation was normal, no exophthalmos, no diabetes insipidus

Blood chemistry	Serum calcium	10.6 mg %
	" phosphorus	5.6 mg %
	" phosphatase	6.5 units
	" protein	6.4 gm %
Serum lipids	Total cholesterol	150 mg %
	Free "	40
	Cholesterol esters	110
	Monoaminophosphatide (lecithin-cephalin)	161
	Diaminophosphatide (sphingomyelin)	117
	Total phospholipids	278

Tissue (dried) Cholesterol content 2.07 mg %

In contrast to the fact that the child was normal in appearance is the roentgen-ray report of her bones "April 9, 1936 The skull, pelvis, femora, tibiae, left scapula, left ulna, right radius, both humeri, the right ninth and tenth and left sixth ribs show smooth sharply defined punched out areas of bone destruction (figures 35, 36) The most extensive changes are seen in the upper ends of the left femur and in the wings of the ilia The head of the left femur is partially destroyed and the shaft of the left femur in the region of the trochanter and neck show multiple vacuolated areas of diminished density with smooth sharp dense margins The lower end of the left femur and the upper end of the tibiae show irregular calcium deposits in lesions which may have been areas of destruction There is a lesion in the left humerus at the junction of the middle and lower third which is quite unlike all the other lesions described It is characterized by moth-eaten bone destruction and extensive periosteal proliferation along about 3 inches of the shaft on the lateral surface No fracture is seen at this point and the soft tissues are normal The bones show a slight degree of osteoporosis and their density is within normal limits except in the region of the lesions described

"Comparing these films with those taken on May 28, 1934 shows definite increase in the number and size of the lesions There has been apparent complete healing in a lesion at the upper end of the left humerus since 1934 It is probable that the lesions in the lower ends of the femora and tibiae are likewise healed but no previous films are available for comparison"

Tissue was obtained by biopsy from the bone marrow of the scapula The amount

of cholesterol in this material is given above. The histological findings (figure 37) as reported by Dr. Granville Bennet of the Harvard Medical School are as follows: "The tissue is very vascular, being traversed by numerous thin-walled capillaries. In most areas there is little supporting tissue between capillaries. However, in a few areas there are larger amounts of connective tissue that indicate slight fibrosis of the bone marrow. The cytological picture of the tissue is greatly varied. Large col-



FIG 35 Case 20 Roentgen-ray of the skull Cystic xanthomatous bone lesions

lections of bone marrow cells are observed in some areas. In other areas the hematopoietic cells are scattered in between good-sized collections of large mononuclear cells which appear definitely abnormal. These cells vary markedly in size and shape. The majority are oval or round. The cytoplasm is usually well stained with eosin dye. In many of the cells, however, the cytoplasm is finely vacuolated or contains brownish pigment, or in some instances it contains both pigment and finely divided vacuoles. The nuclei of the majority of these cells are oval or kidney shaped. Certain areas show marked accumulations of these cells. However, in the majority of fields such cells are scattered in small groups, through the marrow tissue.

"Frozen section stained with Scharlach R show large accumulations of lipid in finely divided globules. This material stains bright red.

"Sections stained with potassium ferrocyanide and dilute HCl show no recog-

nizable iron in the cells that contained brownish pigment in hematoxylin and eosin stained preparations"

Study of this material suggests that the skeletal defects were caused by accumulations of lipid-containing cells and that the lesions represent one form of skeletal xanthomatosis



Fig 36 Case 20 Roentgen-ray of pelvis Xanthomatous cystic bone lesions

Comment and Discussion Case 20 shows xanthomatous involvement of the osseous apparatus only, skull, scapula, ribs, pelvis and extremities. There was no diabetes insipidus and no exophthalmos. The skin was always normal, with no evidence of xanthomata disseminata. The differential diagnosis from multiple myeloma was, therefore, difficult and was only possible by biopsy, which revealed typical foam cells in the bone marrow of the scapula. The chemical examination of the serum showed normal values of cholesterol, as well as phospholipids. The chemical determination of cholesterol in the biopsy tissue from the bone marrow exhibited increased figures for total cholesterol (2 mg per cent) but these were not as high as those found in other tissues by Chiari and Epstein³⁰ (18.58 mg per cent), Kleinmann⁶⁰ (15.8 mg per cent) and Letterer⁶³ (9.6 mg per cent), these were percentages of the dried tissue. In Case 1, 9 mg per cent were found and in Case 9, 13.1 mg per cent. Our Case 20 was unusual insofar as the bones only were involved by xanthomatous changes, but two similar cases have been reported by Fraser.¹⁰

The case of Letterer,⁶³ which also exhibited bone changes without diabetes insipidus and without skin manifestations, showed as an outstanding

feature a xanthomatous involvement of the lymph nodes as in Hodgkin's disease. There were no figures of the cholesterol content of the serum because the patient was diagnosed during life as having Hodgkin's disease,

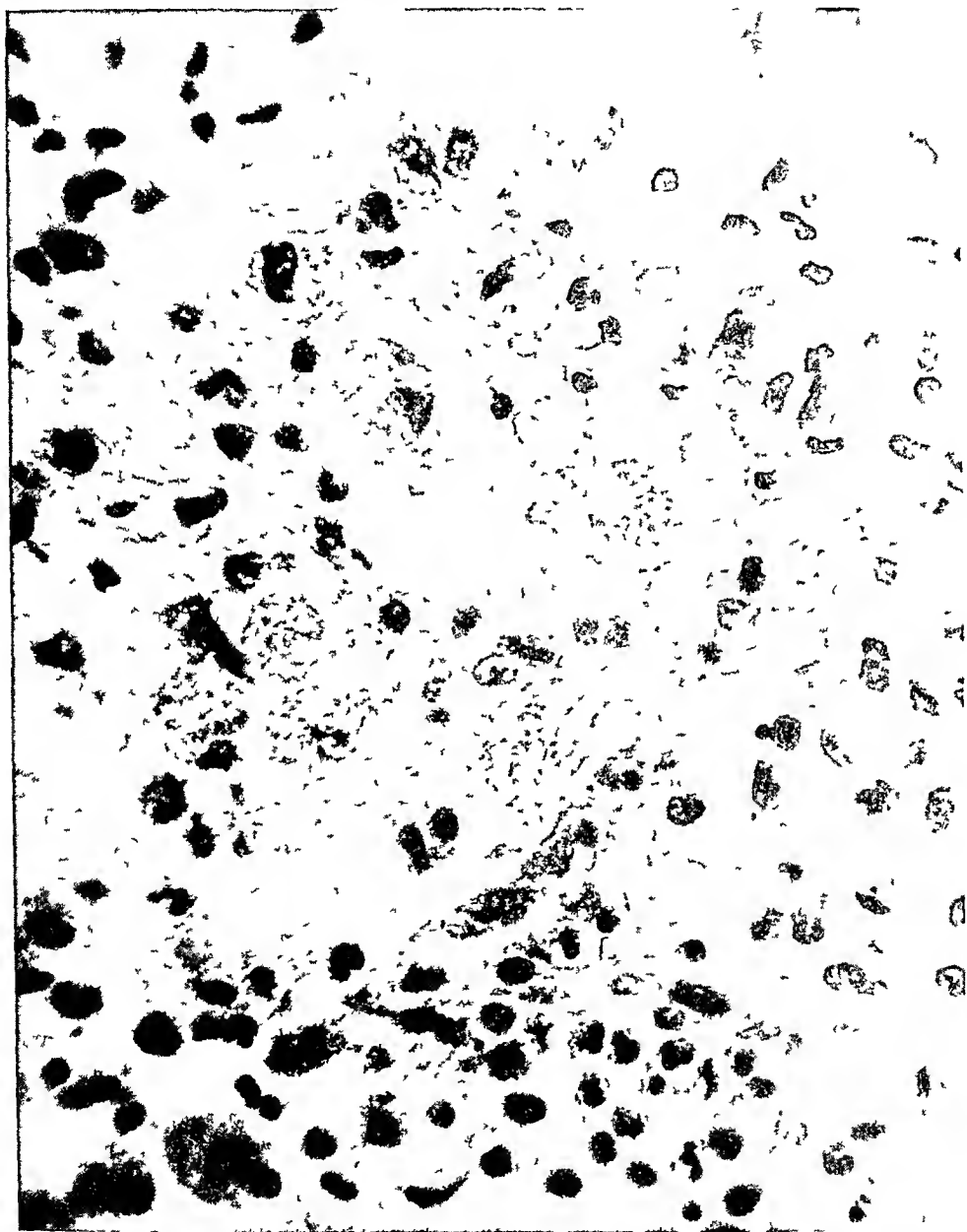


FIG 37 Case 20 Histological picture of a xanthomatous nodule of the bone marrow

although the serum was grossly reported as lipemic. The granulomatous features were so prominent that Letterer speaks of xanthomatous (in the original, xanthoesei) lymphogranulomatosis. Merrill (1920)⁷⁵ described a case of multiple bone lesions with xanthomata tuberosa and plana and

tendon xanthomata The cholesterol content of the blood is reported as very high (figure not given) The published photographs showed the bone cysts to be of very small size and the evidence that they were true xanthomatous bone cysts not convincing There is in the literature not one undoubted case reported of tendon xanthomata and xanthomata plana associated with xanthomata of the bones, whereas xanthomata disseminata are usually seen in such patients affected with osseous xanthomata Further, normal serum cholesterol values are reported in such cases Another doubtful case of xanthomatosis involving only the bones is reported by Snapper and Parisel¹²⁴ Their patient, a girl, showed brown nevi on the skin but not xanthomata The bone biopsy showed changes similar to those in osteitis fibrosa cystica Another biopsy was reported to have shown foam cells According to the paper of Allbright, Butler, Hampton and Smith,^{1a} the case of Snapper and Parisel¹²⁴ does not belong to true osseous xanthomata Two cases reported by Chester²⁸ as lipid-granulomatosis, one a woman of 44, the other, a man of 69, were found to have extensive xanthomata of the bones In neither of these cases was diabetes insipidus or exophthalmos observed during life Xanthomatous involvement of the lungs and pleura was found at autopsy

Our case 20 belongs to those unusual cases of xanthomata where the granulomatous features of the tissues were predominant, and xanthoma cells scarce The low cholesterol values in the analyzed tissue are the chemical expression of this fact However, there is no doubt that, according to the biopsy, Case 20 exhibited xanthomatous involvement of the bones

The attempt has been made in the description of these 20 cases and in the discussion of the literature to distinguish between two clinical groups of primary xanthomatous diseases The characteristic features in the one group are (1) xanthomata plana and tuberosa, (2) tendon and tendon sheath xanthomata, (3) xanthomatous involvement of the wall of the bile duct with xanthomatous biliary cirrhosis, (4) xanthomatosis of the wall of the blood vessels and endocardium, (5) high values of total cholesterol in the serum, increased fraction of lecithin and cephalin, increased fat, (6) eruptive form of skin xanthomata, (7) xanthoma cell nests in the spleen, lymph nodes and liver

The features of the other group are (1) xanthomata disseminata of the skin, mouth and larynx, (2) xanthomatous involvement of the pituitary and tuber cinereum with the features of diabetes insipidus, xanthomata in the brain and medulla, (3) xanthomatous nodules on the dura and orbit, (4) osseous xanthomata, (5) xanthomatous involvement of the lung and pleura with consequent fibrosis, (6) normal or high normal total cholesterol in the serum, normal lecithin and cephalin fraction, normal fat, (7) scattered nests of xanthoma cells in the spleen, lymph nodes and liver (also present in the first group)

The two groups differ in the organs involved as well as in the lipid chem-

istry of the serum The main histological findings in all types of lesions are the same, namely xanthoma cells, granulomatous scar tissue with giant cells and exudate cells, varying according to the age of the lesion We would like clinically to distinguish these two groups of xanthomatous diseases as "hypercholesteremic" and "normocholesteremic" types We must, however, be aware that the underlying disease, that is "essential xanthomatosis," is the same in both groups

Only three cases, where the organs involved by the xanthomatous process comprise both groups in one patient, could be found in the literature (1) Hardaway (1889)⁴⁹, (2) Weidman and Freeman (1924),¹⁴⁹ Griffith (1922)⁴⁶ (case is identical with Weidman and Freeman), (3) Weidman and Stokes (1937),¹⁵⁰ Gitting (1929)^{45a} (case is identical with Weidman and Stokes) Hardaway's patient exhibited xanthomata disseminata (face, neck, axillae, trunk, extremities, as well as mucous membranes of the mouth and larynx), osseous xanthomata of the long bones, xanthomatous lesions in herpes zoster as well as hepatic cirrhosis with jaundice and xanthomata of the tendons Hardaway speaks of a xanthomatous diathesis He suggested, like Quinquaud, 1879,^{95a} who used the expression "diathèse xanthomatique," that xanthoma formation is a "diathetic affection" and that its connection with hepatic disease was entirely secondary or, in other words, that jaundice occurring during the course of the disease was a consequence of "a deposition of xanthomatous tubercles in the liver"

Weidman and Freeman's patient¹⁴⁹ is the most completely studied case, illustrating the combined group, excellent histological photographs of all organs involved are published This nine year old boy showed, as did Hardaway's patient, xanthomata disseminata and xanthomata plana, "hundreds of little nodules on mouth, neck, axillae, elbows, knees, also in the lines of the palms The margins of all four lids have long flat lesions There were several nodules on the side of the head, the underlying bones were depressed and roentgenograms showed small bony defects of the frontal and parietal regions" The boy was jaundiced, polyuric (diabetes insipidus) and had an enlarged liver Total cholesterol 397 mg per cent The post mortem revealed xanthomatous involvement of the skin, brain, pituitary and tuber cinereum, diffuse xanthomatosis of the lung, xanthomatous biliary cirrhosis, xanthomatous changes in the lymph nodes, xanthomata of dura and skull

The third case of the combined type, a girl 6 years of age, reported by Weidman and Stokes,¹⁵⁰ showed tuberous xanthomata in operative scars, and in our opinion the eruptive form of xanthomata, associated with a very high blood cholesterol (1039 mg per cent) (Gitting^{45a} reported in 1928 the same case with a blood cholesterol of 120 mg per cent) There was also diabetes insipidus but no exophthalmos The roentgenogram did not show skull involvement There were xanthomata on the roots of the teeth, jaundice and a large liver No autopsy

CLASSIFICATION OF ESSENTIAL XANTHOMATOSIS

At the present time, primary xanthomatosis is classified by Rowland¹⁰² as embracing skin and mucous membrane, tendon sheath and visceral varieties, also as a separate entity—Schueller-Christian's disease. Buerger²⁵ classifies the disease into three groups (1) essentially osseous, (2) essentially cutaneous and (3) essentially visceral localization. On study of our 20 cases and the reported cases in the literature, it seems to us that the clinical pictures and the anatomical facts do not warrant such a division. The clinical pictures show conclusively that the xanthomatous manifestations of the skin are different in appearance and significance. We tried to point out that certain well characterized forms of xanthomata of the skin are correlated with different xanthomatous manifestations of various organs. Two different groups of primary xanthomatosis are distinguishable without difficulty. Both groups differ, not only in the visceral organs affected and the skin manifestations, but also in chemical findings in the serum (hypercholesteremia on the one hand and normocholesteremia on the other). The description of three cases in the literature, where the features of both groups of xanthomata are found in one patient (combined group) reveals conclusively that primary xanthomatosis is a systemic disease. Primary xanthomatosis (metaplastic reticular cholesterosis) may occur isolated in one organ or combined in two different groups of organs or generalized in all organs which contain reticulum cells and histiocytes.

THERAPY OF ESSENTIAL XANTHOMATOSIS

The two groups of xanthomatous diseases respond differently to therapeutic procedures. The xanthomatous diseases of the hypercholesteremic type show a marked decrease of the hypercholesteremia, as well as a decrease of the other blood lipids after a period of cholesterol and fat-poor diet. Such diets have been described by me¹³⁷. They contain only vegetable fats because plant sterols are not absorbed (Schonheimer¹¹⁵). The xanthomatous diseases of the normocholesteremic type do not respond to diet treatment at all. We applied in both groups, in addition to the diet treatment, small doses of Thyroidin, one gram daily, with good effect in the hypercholesteremic group, while in the normocholesteremic group an influence on the cholesterol content of the serum was not evident.

The osseous xanthomata and the dura xanthomata of the cases of the normocholesteremic type respond to roentgen-ray therapy very satisfactorily according to Sossman and other authors. Whether the other organs (skin, lungs, brain) belonging to the symptom complex of the normocholesteremic type react to roentgen-ray favorably is not known. The skin xanthomata belonging to the group of the hypercholesteremic type, however, as well as the tendon xanthomata, are not influenced at all by roentgen-ray.

SECONDARY XANTHOMATOSIS

The two cases to be reported here were observed at the Deaconess Hospital by Dr Elliott P Joslin and his associates, to whom I am indebted for the privilege of publishing the records

Case 21 The patient was in acidosis when first seen by Dr Joslin, January 15, 1934 Glycosuria 7.4 per cent, blood sugar 250 mg per cent, insulin 56 units daily He showed lipemia retinalis and an eruption characterized by nodular pustules, surrounded by narrow pink zones

The localization of these nodular-pustular eruptions which come and go is usually all over the body except for the scalp The nodular pustules vary in size from a small pinhead to a grain of wheat There are a few larger lesions formed by the confluence of adjacent lesions The lesions for the most part consist of a light yellow tip upon an inflammatory reddish base, which may change color in due course to violet and brown Except on close inspection, they would be taken for true pustules Indeed, physicians and patients have opened them in an effort to remove the yellow material seemingly present on the tip and have been puzzled to get only blood and a little white serum It is noticeable that the lesions do not always have a yellow tip, therefore the etiology is usually not recognized Some of the lesions are excoriated by scratching, due to itching These lesions come and go In this case, they had disappeared within five months after insulin and diet treatment was instituted which had effected also a complete disappearance of the lipemia

Date	Cholesterol	Blood Sugar
1/15/34	1600	0.21
1/16/34	1520	0.21
1/17/34	1344	
1/18/34	1376	0.21
1/19/34	1248	0.21
1/20/34	1248	0.27
1/22/34	1184	0.27
1/27/34	792	0.19
2/3/34	416	0.15
2/17/34	294	0.18
3/15/34	175	0.19
5/3/34	172	0.26
6/9/34	205	0.16

Case 22 Patient 32 years of age, seen September 18, 1934 Weight 132 pounds Insulin 52 units Feels fine Diabetes discovered in December 1925 The diagnostic remark was "a mild diabetes, but not very cooperative" Eight years later the patient was seen again At this time, April 29, 1933, hard xanthomatous lumps were found in the right heel Plasma cholesterol was 644 mg per cent, blood sugar 120 mg per cent On August 17, 1934, simultaneously with lipemia and definite lipemia retinalis, an eruption appeared of many small yellowish papules scattered diffusely on arms, chest and lower back Glycosuria 3.3 per cent Blood sugar 220 milligrams Plasma cholesterol 768 milligrams

Comment and Discussion We owe the first description of this kind of eruptive xanthomata to Addison and Gull,¹ who described its occurrence in a diabetic in the historical paper already mentioned as giving the first description of xanthomata plana and tuberosa with biliary cirrhosis Their description follows

"The eruption somewhat suddenly appeared on the arms In the course of

ten days, it had extended over the arms, legs and trunk, both anteriorly and posteriorly, also over the face and into the hair, it consisted of scattered tubercles of various sizes, some being as large as a small pea together with shining, colorless papules. They were most numerous on the outside and back of the forearm, and especially about the elbows and knees, where they were confluent. Along the inner side of the arms and thighs, they were more sparingly present, and entirely absent from the flexures of the larger joints. Besides the compound character produced by the confluence of two or three tubercles, which appeared to be such, as shown by the prominent whitish nodules upon them, some looked as if they were beginning to suppurate, and many were not unlike the ordinary molluscum, but when incised with a lancet, they were found to consist of firm tissue, which on pressure gave out no fluid save blood.

"They were of a yellowish color, mottled with a deepish rose tint, and with small capillary veins here and there ramifying over them. They were accompanied with a moderate degree of irritation, hence the apices of many were rubbed and inflamed."

This eruptive form so excellently described almost ninety years ago was characterized as "xanthoma diabeticorum." Many authors designate as xanthoma diabeticorum not only the eruptive form, which comes and disappears simultaneously with the lipemia, but also xanthomata tuberosa and plana, which are persistent. This confusion results from the fact that xanthomata tuberosa and plana are observed simultaneously with a mild diabetes as described in our Case 22 and in Case 4. In these cases, xanthomata tuberosa are features of primary xanthomatosis, when at the same time as the skin, visceral organs are involved. Xanthomata diabeticorum on the contrary are not the cause but the sequel of a complication in diabetes. This complication is lipemia. Xanthomatosis diabeticorum, that is the eruptive form of xanthomata, occurs not only in high lipemia during severe diabetes, but also in primary xanthomatosis, if high lipemia is present. This fact is evident in the three cases with xanthomatous biliary cirrhosis without diabetes but with lipemia. The eruptive form of xanthomata described and pictured in these cases of primary xanthomata is identical in appearance as well as in its transitory character with the eruptive form of xanthomata occurring in severe diabetes without primary xanthomatosis, and known as xanthomata diabeticorum. In the above described Case 22, tuberous xanthomata and mild diabetes were present for many years until rather suddenly lipemia was noted as lipemia retinalis and the eruptive form of xanthomata occurred. The eruptive form of xanthomata and lipemia disappeared, but the xanthomata tuberosa and hypercholesteremia persisted. A similar case is described by Major^{71, 72} (1924), who pointed out that xanthomata diabeticorum is connected with lipemia and not primarily with diabetes.

We should like to emphasize that the eruptive form of xanthomata (xanthoma diabeticorum) is etiologically entirely different from all xanthomata due to primary xanthomatosis. The latter is a systemic disease. The eruptive form is a symptom of lipemia and may occur in diabetic

lipemia as well as in lipemia during xanthomatous disease as in xanthomatous biliary disease

We have already pictured the histological findings of the eruptive form of xanthomata (figure 22) In the photographed specimen xanthomata cells are not found But there are reports in the literature that besides the signs of inflammation, there are found some rare xanthoma cells R H Major points out this difference from true xanthomata He described his findings as follows

"A section from one of the excised nodules showed marked evidence of inflammation The corium was thickened, extensive keratinization had taken place, there were areas of small, round-cell infiltration, marked fibrotic changes present and the characteristic large xanthoma cells were recognized with difficulty"

The xanthomatous lesions described by Urbach¹⁴² as extracellular cholesterosis should now be discussed "The essential lesions are lentil-sized, hard translucent nodules, sometimes with a central blister After one or two days they become blue-violet, generally with a yellow center and later still reddish-brown Sometimes at the beginning the eruptions resembled erythema multiforme Some of the lesions disappeared after a few days and even nodes of long duration regressed considerably under roentgen-ray" The histological findings in Urbach's nodules of extracellular cholesterosis exhibit vascularity of the cutis with damage to the vascular endothelium and infiltration with round and spindle cells In none of the preparations was there the slightest indication of foam-cell formation The lipid was entirely extracellular, first around the vessels and later in the whole cutis The lipid was found by staining and chemical analysis of the lesion, which revealed a cholesterol to cholesterol ester ratio of 3 : 1 in contrast with true xanthomata tissue of 1 : 1.5 These figures are impressive indeed But if we really considered the material chemically analyzed in the case of the eruptive xanthomata (extracellular cholesterosis), the value of those figures is doubtful because the quantity of material must have been minimal and the quality of material is varying and uncontrollable in view of the minimal amount of pathological tissue and the amount of healthy tissue chemically examined in the same specimen Chemical analysis of pathological tissue is of value only if a large amount of characteristic tissue like true xanthomata can be analyzed Be the value of the chemical findings what it may, the clinical description of the lesions of "extracellular cholesterosis" by Urbach is in conformity entirely with the clinical appearance of eruptive xanthomata first described as xanthomata diabeticorum by Addison and Gull, and many subsequent authors

The differential diagnosis of the eruptive form of xanthomata from xanthomata disseminata which are true xanthomata, that is, the skin manifestations of a systemic disease which simultaneously involves a group of organs, should not be difficult The eruptive form is scattered, never in ridges, never mulberry-like or in warty clusters, nor are they pedunculated

The lesions are isolated or in small groups. The color of the lesions in xanthomata disseminata is lemon yellow or in older lesions a deep reddish brown, mahogany-like. They grow in ridges and clusters with localization around the neck, axillae, and in the bend of elbows and knees.

Sometimes it may be difficult at first to differentiate the eruptions from erythema multiforme, but the colorations and vascularization of the nodule is characteristic after a few days so that the eruptive form of xanthomata cannot be easily mistaken. The blood findings of high cholesterol (the ratio of cholesterol to cholesterol esters may be normal in diabetes, and reversed in xanthomatous biliary cirrhosis), high fats and lipemia confirm conclusively the diagnosis already made clinically.

That the eruptive forms of xanthomata and xanthomata diabeticorum are identical should be emphasized. Hyperlipemia and hypercholesteremia result in this kind of skin eruption, which we consider as secondary to the high grade of lipemia occurring in the course of severe diabetes mellitus or in the course of xanthomatous biliary cirrhosis. Therefore, the skin manifestations of primary xanthomatosis must be differentiated from the eruptive form of xanthomata, the so-called xanthomata diabeticorum, which are classed in the group of secondary xanthomata. Xanthomata tuberosa, on the other hand, are independent features of primary xanthomatosis and occur at times with diabetes mellitus. Their presence in diabetes is an indication that the systemic primary xanthomatous disease involves also visceral organs, possibly the pancreas.

Severe lipemia, during diabetes mellitus, produces, not only in the skin but also in other organs, changes which are histologically very similar to those of xanthomatous disease. This kind of xanthomatous change occurring in the spleen and lymph nodes belongs also to the group of secondary xanthomata because the lipemia is the primary occurrence and the xanthoma cell formation is due to a secondary deposit in reticular cells and histiocytes. W. H. Schultze¹²¹ (1912) described first "large cell hyperplasia of the spleen during lipemia" and shows that little nests of xanthoma cells occur in the spleen as a result of lipemia in diabetes mellitus. Lutz,⁶⁷ Williams and Dresbach,¹⁵⁸ Pick,⁸⁴ Margaret Smith,¹²³ W. Schondorff,¹⁰⁹ S. Warren and Root¹⁴⁷ describe such large cell hyperplasia in diabetes with lipemia. We are inclined to classify the case which Lubarsch⁶⁶ described in 1918 under the title "Generalized Xanthomata and Diabetes" as the most outstanding example of this group of secondary xanthomatosis. This patient suffered and died of severe diabetes with lipemia. The liver, spleen, kidneys and especially lymph nodes and the walls of the lymph vessels exhibited large patches of xanthoma cells (lymphangitis xanthomatosis). There was no xanthomatosis of the skin but xanthosis of the skin was found. Xanthosis of the skin is almost always associated with the first group of primary xanthomatous diseases of the hypercholesteremic type (Cases 4, 6, 9, 11), but xanthosis of the skin has nothing to do with xanthoma formation.

Xanthosis, first described by von Noorden⁸¹ in diabetes mellitus, is a symptom which may occur without diabetes in all conditions of lipemia and even without lipemia if carotene is increased in the serum. The significance of the coincidence of hypercholesterolemia and hypercarotinemia is unknown. Xanthoma cell formation in the reticular apparatus was a secondary process due to lipemia similar to the more localized forms described in the spleen and in lymph glands. Certainly we cannot prove that Lubarsch's case belongs to this group of secondary xanthoma cell formation. However, the complete absence of skin xanthomata of both groups (xanthomata tuberosa and plana on the one hand and xanthomata disseminata on the other hand) while xanthosis was present, in addition to the clinical course of the disease is highly in favor of this assumption. We have already suggested above that Buerger and Grutz' cases of hepatosplenomegaly without jaundice but with extreme lipemia may belong to this group of secondary xanthomatosis resulting from lipemia. The lipemia in these cases is of unknown origin. Chronic cirrhosis of the pancreas may result in such extreme lipemia, but in contrast to the lipemia in diabetes mellitus, this lipemia condition is scarcely influenced by diets poor in fats. Attempts already made by different authors (Anitschkow,^{3, 4, 5} Kawamura⁵⁷ and McMeans⁷⁰) to reproduce xanthomatosis by the feeding of cholesterol, or to reproduce Gaucher's disease by intravenous injection of cerebroside (Kimmelstiel and Laas⁵⁹) and Niemann-Pick's disease by injection of phosphatides (H. Baumer and G. B. Gruber)¹⁴ lead to similar histological pictures in the spleen and lymph nodes as described by Schultze and others, as "large cell hyperplasia of the spleen during lipemia." It is evident that the reticular cells and the histiocytes are able to take up out of the blood, cholesterol as well as cerebroside and diaminophosphatides. In so doing, these cells change in appearance and assume the shape of foam cells. This procedure of injection of lipids, however, does not reproduce either the clinical syndrome or the complex anatomical picture of any of these "lipoid diseases," but it does reproduce histologically similar organic changes in the spleen, lymph nodes, and in extreme cases also in the liver (described by Schultze¹²¹ and others) to those that occur in association with lipemia in diabetes mellitus. It may well be that the mechanism of xanthoma cell formation in essential xanthomatosis is entirely different from the procedure which only attempts to increase the lipids in the blood by feeding or intravenous injection.

THE ETIOLOGY OF XANTHOMA FORMATION

The different clinical symptoms of essential xanthomatosis having been presented, the etiology of xanthoma formation in this systemic disease will now be discussed.

Waldeyer (1871)¹⁴⁶ considered the cells of xanthomata plana, afterwards called foam cells, to be embryonal cells which had the possibility of forming different kinds of fats and of releasing the fat by degeneration.

Virchow¹⁴⁵ described under the heading "xanthoma multiplex mulluscum lipomatoïdes," xanthomata disseminata of the skin as little benign neoplasms. Following the opinion of Virchow, xanthomata in general were considered in the literature to be "benign tumors." "*Ce sont donc les cellules endothéliales des espaces lymphatiques qui par leur prolifération, forment la tumeur xanthomateuse*" (classified as "endotheliome adipeux" by de Vincentis¹⁴³). Ponsgen,^{89, 90} Koebner⁹¹ accept the opinion of Waldeyer,¹⁴⁶ that cells which remained in an embryonal stage produced by their proliferation and adipose metamorphosis a so-called "embryonal lipoma" which is identical with the xanthomata. Torok¹³⁸ says that it is better not to classify xanthomata as true tumors but as abnormality of formation "*il (xanthoma) se forme du tissu à une endroit hétérotopique et il est constitué en raison même de cette hétérotopie par des cellules adipeuses à évolution interrompue incomplète*" (embryonale).

Pinkus and Pick (1908)^{87, 88} found the fat substances in the xanthoma lesions to be doubly refractile lipids, cholesterol and cholesterol esters. These authors suggested that hypercholesteremia may be the genesis of xanthomatosis. "Cholesterol infiltration of certain cells takes place because of an increased cholesterol supply from the blood." This hypothesis was advanced after Aschoff^{3, 9} and his pupils had demonstrated that reticulo-endothelial cells were able to take up from the blood different kinds of dyes, as well as fat-like substances. Anitschkow^{3, 4, 5} in Aschoff's Institute found that by feeding rabbits cholesterol, foam-cells could be produced. On the other hand he was able to demonstrate that the same cells which changed to foam-cells also took up substances foreign to the body such as dyes. Indeed, these cells which have the characteristic of storing doubly refractile substances, as well as dyes, belong to those cells which Aschoff⁹ classifies as the reticulo-endothelial system. Because hypercholesteremia was believed to be essential for xanthoma cell formation it was natural to assume that the surplus of cholesterol in the serum due to a general disturbance of the cholesterol metabolism is taken up and stored by the reticulum cells, and results in a pathological change of the tissue forming xanthomata. This hypothesis is widely accepted in the literature. The proof, however, that there exists such a disease as a general metabolic disturbance of the cholesterol metabolism, which is the prerequisite of this assumption, is lacking. Appreciating this weak point of this hypothesis, Bloch¹⁸ and Schaaf¹⁰³ explain that cholesterol represents only one element in a very complex mixture of fat and lipids in the serum. "This mixture of lipid constituents does not exist in the serum in a dissolved form, but in the form of a finely dispersed emulsion. The normal proportion of all the lipid constituents must be maintained in the blood. If the proportion is changed in any direction, i.e. if the proportion of cholesterol to lecithin or to cerebrosides or sphingomyelins is altered, the result according to the laws of the colloid theory is a disturbance in the stable aqueous lipid emulsion which the serum represents

The particles become coarser, the emulsion separates, and finally there is a precipitation of one or all of the individual constituents in the blood and tissues and a deposit of material, so that xanthomatosis results." This hypothesis of Bloch¹⁸ and Schaaf¹⁰³ has also as a prerequisite an extra-cellular general metabolic disturbance of the lipids, which results secondarily in a deposit of lipids in the reticular cells and the tissue. There is neither proof of a colloid decomposition of the serum or cell fluids resulting in precipitation nor any evidence that a disproportion of the lipids in the serum or tissue may lead to a flocculation of the colloid mixture. Deposits of lipids, especially cholesterol, are found in deteriorated tissue and in places where cells containing cholesterol undergo destruction. Up to the present we do not know of a spontaneous decomposition of a colloidal system of lipids in the serum even when the constituents of this system are markedly changed in their relation to each other. The colloid systems protected by different mechanisms in the organism are not to be compared with colloid systems prepared in the test tube because it is only partially and inadequately possible to copy the constituents of the colloid mixture in the body. The hypothesis of Bloch and Schaaf which adds to the assumption of extra-cellular disturbance of the lipid metabolism, a second hypothesis which has not been proved at all, does not stand critical analysis from the chemical point of view.

There remains to discuss as the main question, whether essential xanthomatosis is due to a general metabolic disturbance of cholesterol metabolism, which leads to an increased cholesterol supply to the reticular cells and a consequent storage of cholesterols and lipids in these cells (cholesterol infiltration of L. Pick^{85, 88}), or whether the metabolic disturbance is an intracellular metabolic disturbance confined to the reticular cells themselves, which may become xanthoma cells not by an increased supply but as the result of an intracellular metabolic disorder. The problem is, therefore, whether essential xanthomatosis is due to a disturbance of the intermediary cholesterol metabolism or whether it is caused by an intracellular metabolic disorder limited to certain reticular cells. Considering the mechanism of an intermediary disorder of the cholesterol metabolism, four possible processes of cholesterol metabolism may play a part.

(1) There may be a diminished disintegration of cholesterol in the intermediary metabolism. The xanthomata would then be the expression only of its retention and storage.

(2) There may be a diminished excretion and output of cholesterol and coprosterol in the feces. In such a case the xanthomata would be, as in the first process suggested, the result of retention and storage of cholesterol.

(3) The equilibrium between cholesterol and cholesterol esters may be disturbed so that sufficient cholesterol esters are not formed to transport an adequate amount of cholesterol. For the same reason the other lipids,

especially the phospholipids, may be involved and a disturbance of the lipid mixture may result

(4) There may be an increased synthesis of sterols. This increased synthesis may occur in organisms as a whole, and the sterols ubiquitously synthesized in the body are taken up out of the blood by reticular cells and stored. Or the increased cholesterol formation is performed by certain reticular cells which are able to synthesize and release cholesterol, but in the process as the result of an intracellular imbalance reticular cells assume the appearance of xanthoma cells. On the basis of the physiology of the intermediary cholesterol metabolism, which we have discussed earlier, we believe we are able to answer these four questions as to whether or not essential xanthomatosis is the result of a disturbance of the intermediary cholesterol metabolism.

The first assumption suggests a diminished disintegration of sterols in the intermediary metabolism. We have shown in our physiological discussion that there is no disintegration of cholesterol in the intermediary metabolism. Neither bile acids nor other sterols occurring in larger quantities in the organism are derivatives of cholesterol disintegration. The human organism is able to synthesize the sterol skeleton but cannot disintegrate it by means of fermentative processes.

In the second suggestion the question was raised whether a decrease of the cholesterol excretion could explain the essential xanthomatosis. Such an assumption should be easily answered by determining the cholesterol balance, but unfortunately the determination of cholesterol excretion in the feces cannot decide conclusively the cholesterol balance, because an uncontrollable amount of cholesterol may be destroyed by bacteria of the feces (according to Bertha Ottenstein). On the other hand, we have demonstrated that a diet free of animal sterols decreases the cholesterol content of the blood in cases of tendon xanthomata as well as in xanthomatous biliary cirrhosis. On the basis of an experiment carried out on a patient with tendon xanthomata where the total cholesterol dropped from about 800 mg per cent to almost normal values, Schonheimer and I have been inclined to believe that retention of sterols plays an important part in formation of xanthomata. The opinion was expressed that these patients behave like herbivorous animals, which can absorb but not excrete cholesterol. However, we had to change our minds because several of our patients (Cases 1 and 9) on a cholesterol-free diet showed insufficient reduction of the cholesterol in the serum, and we found that xanthomata tuberosa as well as tendon xanthomata were not altered even when the blood cholesterol had returned to almost normal values. The most important argument against the assumption that a disturbance of cholesterol output is the main cause of essential xanthomatosis is the fact that in the group of xanthomatous diseases characterized by xanthomata disseminata of the skin, involvement of the brain (diabetes insipidus), involvement of the bones, lungs and lymph

nodes, the cholesterol values in the serum were normal or high normal. Even in the other group, the hypercholesteremic type, which comprises xanthomata tuberosa and plana, tendon xanthomata, xanthomatous biliary cirrhosis, etc., we were able to find almost normal cholesterol figures (Cases 2 and 11) with beginning tendon xanthomata. A diminished output may play some rôle in the clinical course of essential xanthomatosis, but it is evident that this is not the main cause of this systemic disease.

The third possibility was a disturbance in cholesterol-ester formation or of a disproportion of cholesterol to phospholipids. In the literature and in our cases, the increase of total cholesterol, where there is an increase, is due to an increase of esters. The only exception to this finding of normal or high cholesterol esters in xanthomatosis was in patients with xanthomatous biliary cirrhosis where we found an inversed ratio of cholesterol to cholesterol esters in the serum. This is due to the liver damage and not to the xanthomatous disease (Thannhauser and Schaber¹³¹). The normal or high cholesterol esters in the blood and the high content of cholesterol esters in xanthomatous tissue show conclusively that there is no disturbance of ester formation which could cause difficulties in cholesterol transportation and lead to an abnormal deposit of cholesterol. Only in old granulomatous scar tissue of xanthomata, as in tendon xanthomata, free cholesterol prevails over ester-cholesterol, and sometimes crystallizes in the tissue. This tissue may have partially softened into a yellowish detritus. In the scars of these xanthomata foam cells are still scarcely found having been replaced by granulomatous tissue or softened to a yellowish, semi-fluid mass. Cholesterol esters are absorbed easier from such broken down foam cells while free cholesterol remains and crystallizes "in loco" (Figure 4, Case 1).

The figures for fat, cholesterol, cholesterol esters, monoaminophosphatides (lecithin and kephalin) and diamminophosphatides (sphingomyelins) of our series of cases are summarized here. These findings demonstrate that in xanthoma diseases of the hypercholesterol type, an increase of total cholesterol is usually accompanied by an increase in fat and monoaminophosphatides (lecithin and kephalin), while in the group of xanthomatous diseases of the normocholesteremic type, fat and monoaminophosphatides are also normal. We would like to infer from these figures that xanthomata formation is *not* caused by a disproportion of the lipid mixture in the serum, because in the group of xanthomata without an increase of cholesterol, the fat and monoaminophosphatides are normal, and in the group of xanthomata with high cholesterol, fat and monoaminophosphatide are increased proportional to the sterols.

The fourth suggestion deals with the question as to whether an increased cholesterol synthesis carried out everywhere in the organism and followed by a consequent storage of cholesterol in the reticular cells is the cause of essential xanthomatosis. Such an increased cholesterol synthesis as an expression of a general metabolic disturbance should lead in all clinical

	Total choles- terol mg %	Free choles- terol mg %	Choles- terol esters mg %	Total P Lipid mg %	Diamino- phospha- tide (sphingo- myelin) mg %	Mono- amino- phospha- tide (lecithin and cephalin) mg %	Total fat as fatty acids mg %
Normal	110-220	40-80	70-140	200-350	100-150	100-150	200-400

Essential Xanthomatosis of the Hypercholesteremic Type

Case No							
1	308	240	128	375	265	110	
2	210	107	103	330	180	150	
4	476	125	351	437	243	194	1088
5	276	75	201	290	81	209	527
6	216	50	166	309	112	197	
7	265	107	158	450	150	300	577
8	533	129	404	394	132	262	585
9	667	203	464	448	194	254	484
11	282	97	185	303	137	166	471
12	400	100	300				471
13	500	183	317	632	83	549	

Essential Xanthomatosis of the Normocholesteremic Type

18	208	74	134	260			290
19	195	67	128	650	84	566	276
20	150	40	110	278	117	161	
23	191	52	139	228	30	198	320

syndromes of essential xanthomatosis to hypercholesteremia. Hypercholesteremia is, however, found only in one group of xanthomatous organ involvement, while the other group shows a normal amount of cholesterol, in spite of the fact that the same histological constituents are found in both groups. This is definitely against the assumption that xanthomata result from a general metabolic disturbance of cholesterol synthesis and favors the idea that we have to deal with a local cellular metabolic disturbance which may involve one organ only in a small area or groups of organs far apart.

In considering the four possible general disturbances of intermediary cholesterol metabolism discussed above, the following statements can be made. There is no definite proof to justify the assumption that primary essential xanthomatosis is caused by a disorder of the intermediary cholesterol metabolism. The generally accepted theory of L. Pick^{86, 87, 88} which suggests a general disturbance of the cholesterol metabolism followed by a secondary deposit of cholesterol in the reticular cells as the cause of essential xanthomatosis is untenable, since the experiments concerning the normal metabolism of cholesterol do not give the slightest evidence of an inter-

mediary disturbance of cholesterol metabolism. We would rather believe that the metabolic disturbance of the cholesterol is localized in those cells themselves which are called xanthoma cells after their content. Besides the reasons already mentioned, the experiments of Biedermann and Hoefler¹⁷ speak in favor of our suggestion of a localized cellular metabolic disturbance. These authors used tissue cultures of tissue prepared from xanthomatous nodules. They were able to demonstrate that the xanthoma cells of the cultivated tissue increased and emigrated. Some of the cells which had grown were identified as xanthoma cells by their content of doubly refractile substance.

It is evident from these experiments that the xanthoma cells themselves form the doubly refractile substance and a further proof for the genesis of xanthoma cells by an intra-cellular metabolic disturbance is added by the analogy which primary essential xanthomatosis bears to the other diseases of lipid metabolism, namely Gaucher's and Niemann-Pick's disease. In all three of these diseases large cells with fatty content arise in different organs. In essential xanthomatosis these cells contain cholesterol and other lipids. In Gaucher's disease these cells contain cerebroside, while in the Niemann-Pick's disease the content of these cells consists of diaminophosphatides (sphingomyelins). According to the suggestion of L. Pick, it was generally assumed that these three diseases were caused by the storage (infiltration) in the reticular cells of these lipids produced in excess by the intermediary metabolism of the organism. Concerning Niemann-Pick's disease, Baumann¹⁸ has already demonstrated that the content of total phospholipids (mono- and diaminophospholipids) is normal and even lower than normal in the blood. The sphingomyelins, however, are found in abnormal quantities only in the Niemann-Pick cells. In Gaucher's disease, Thannhauser, Reichel, Dameshek and Walcott [unpublished] were able to prove in four cases, that only traces of cerebroside were present in the serum of these patients, as is the case in normal serum. These investigations show that at least for Gaucher's disease, but probably also for Niemann-Pick's disease, the lipid substances involved in the particular disease are not formed in the intermediary metabolism and secondarily deposited in the reticular cells, but are formed and stored in the cells themselves. Gaucher's and Niemann-Pick's disease may, therefore, be considered as due to an imbalance of intra-cellular ferments (Thannhauser and Reichel^{18b}). We believe essential xanthomatosis, which belongs to the same group of lipid diseases, to be analogous to the above two diseases in that it is caused by an intra-cellular metabolic disturbance of certain reticular cells. In these cells cholesterol especially, but also other lipids, are found to be increased and stored, so that the xanthoma cells result.

In assuming a cellular disturbance to be the etiology of primary essential xanthomatosis, we return to the view of former investigators, Waldeyer,^{14b} de Vincentis,^{14c} Hallopeau^{46a} and Torok¹⁸⁸. According to these authors

the xanthoma cells are fat cells with embryonal qualities. With present day interpretations, we would say that these embryonal reticular cells, as far as their metabolism is concerned, are able to form *all* kinds of lipids. At that time the knowledge of metabolism was not sufficiently advanced to recognize the disorder which produced the xanthoma cell, as a cellular metabolic disturbance. The former assumption that the disorder is due to an embryonal metaplasia of certain cell groups is, however, identical with the idea that a cellular disorder is the cause of the disease "essential xanthomatosis."

To clarify further our interpretations of the mechanism of these cellular diseases, we may speak of essential xanthomatosis as "metaplastic reticular cholesterosis," of Gaucher's disease as "metaplastic reticular cerebrosidosis," and of Niemann-Pick's disease as "metaplastic reticular sphingomyelinosis."

The groups of secondary xanthomatous diseases are to be distinguished in principle from primary essential xanthomatosis (metaplastic reticular cholesterosis). In contrast to the primary essential xanthomatosis, which is a systemic disease resulting from an intracellular metabolic disturbance, the secondary xanthomatosis (eruptive form of xanthomata, formation of nests of xanthoma cells in the spleen, lymph glands and liver, large cell hyperplasia of Schultze) is a disease which is due to a storage of lipids which the reticular cells take up from the blood. An increase of cholesterol and other lipids in the serum as in lipemia during diabetes mellitus or as in lipemia of other origin, is the prerequisite of secondary xanthomatosis.

By suggesting that the formation of true xanthoma cells is due to an intracellular metabolic disorder of the reticular cells, we may explain the fact that xanthoma cell formation may occur independently of "essential xanthomatosis," as it does in localized tumors which have nothing in common with the systemic disease "essential xanthomatosis." Indeed, xanthoma cells are observed in different kinds of local tumors, such as fibrosarcoxanthomata, nevoxanthoendothelioma (Montgomery and Osterberg), etc.

As a result of the above study, and in order to clarify interrelationships between the type of xanthomata of the skin, and the various clinical patterns associated with each type, the following classification of xanthomatous diseases is offered.

CLASSIFICATION

- I *Primary essential xanthomatosis* (metaplastic reticular cholesterosis)
 - A Primary essential xanthomatosis of the hypercholesteremic type
 - 1 Xanthomata of tendons and tendon sheaths *
 - 2 Xanthomata tuberosa and plana
 - 2a *Forme fruste*
 - 3 Xanthomatous biliary cirrhosis resulting from xanthomatosis of the bile ducts

* The recent papers of van Bogaert and Epstein describe the combination of tendon xanthomata with xanthomatosis of the central nervous system. We are inclined to classify this new syndrome under the group of tendon xanthomata until more cases of this type have been analyzed.

- 4 Xanthomatosis of the endocardium and blood vessels
- 5 Eruptive form (if excessive lipemia is present) of skin xanthomata
- 6 Scattered nests of xanthoma cells in the spleen, liver and lymph glands (these may also be present in group B)

B Primary essential xanthomatosis of the normocholesteremic type

- 1 Xanthomata disseminata of the skin (localized all over the body, neck, axilla, bend of knees and elbows, groins, mouth and larynx)
- 2 Osseous xanthomata of the skull, scapula, pelvis, extremities and orbit
- 3 Xanthomatous involvement of pituitary and tuber cinereum with features of diabetes insipidus Xanthomata of brain, medulla and dura
- 4 Xanthomatous involvement of the lung and pleura with consequent pulmonary fibrosis
- 5 Scattered nests of xanthoma cells in the spleen, lymph glands and liver (these may also be present in group A)

C Primary essential xanthomatosis of the combined type (Cases of Hardaway, Weideman and Freeman, Weideman and Stokes)

II Secondary xanthomatosis due to lipemia

- 1 Eruptive form of xanthomata Xanthomata diabeticorum
- 2 Nests of xanthoma cells in the spleen, lymph glands and liver with and without hepatosplenomegaly (Schultze's large cell hyperplasia in the spleen during lipemia)
- 3 Xanthomatous lymphangitis (Lubarsch)

III Localized xanthoma cell formation in true tumors (Nevoxantho-endothelioma, fibrosarcoxanthoma, etc)

SUMMARY

- 1 The physiology of the cholesterol metabolism and its interrelationships with xanthomatous diseases is discussed
- 2 A critical review of the literature is presented
- 3 Twenty-two cases illustrating the different features of xanthomatous disease are described
- 4 On the basis of the above study, three different symptom-complexes of primary essential xanthomatosis are presented and differentiated and a classification offered Secondary xanthomatosis due to lipemia is distinguished from primary essential xanthomatosis
- 5 Xanthomatous biliary cirrhosis and its relation to xanthomatous bile duct disease is described

6 The eruptive form of xanthomata (xanthomata diabeticorum) is shown to occur not only in hypercholesteremia in diabetes mellitus, but also in xanthomatous biliary cirrhosis, xanthomata tuberosa and tendon sheath xanthomata if excessive hypercholesteremia is present

7 Xanthomata disseminata has been shown to be characteristic only of the second (normocholesteremic) group

8 It is shown that the general assumption that essential xanthomatosis is a storage disease of the reticular cells due to a disturbance of the general intermediary metabolism of cholesterol, is not in conformity with the physiological and clinical findings. Our studies suggest that essential xanthomatosis is a cellular disease of reticulum cells caused by an intracellular disorder of their cholesterol metabolism

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CASE REPORTS

TORULA MENINGO-ENCEPHALITIS, A CASE REPORT *

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SINCE the contribution of Freeman¹ on torula infection of the central nervous system, increasing attention has been paid to this interesting condition. Recently Levine² has again reviewed the literature, adding 17 more cases, including two of his own, bringing the total number to 60. The present case is reported, not so much because of the rarity of the condition but to add a new and as yet unreported manifestation of the infection, a cicatrizing lesion of the brain.

CASE REPORT

The patient, a white male 30 years old, was admitted to City Hospital on March 15, 1935, complaining of severe headache and abdominal pain.

Past History At the age of two years, he had scarlet fever. At 12, an enlarged cervical gland was diagnosed as tuberculous and treated by injection, possibly with an iodized oil. A biopsy, however, was not performed. At 14 and 16 there occurred attacks of pneumonia. From 26 to 28, he had severe epileptiform seizures which had continued in increasing frequency since then. He was drinking heavily when the seizures first appeared and they were attributed to this fact.

Present Illness One week before hospitalization, he began to have excruciating headache, the pain radiating from the eyes to the temporal regions. After three days, it was associated with vomiting. Both symptoms increased in severity to the time of admission. There were no other pertinent data.

Physical Examination He was a well developed and well nourished young man, extremely restless because of the headache. Mentally he was clear and cooperative. There was general hyperreflexia. Muscular, sensory and equilibratory tests were all normal. Abdominal reflexes were present. Pathological reflexes were absent. The pupils were equal, regular and reacted normally to light and accommodation. There were no ocular palsies. The fundi were normal. Except for a slight tachycardia, the other systems were entirely negative. The temperature was 99° F, pulse 60, respirations 20, blood pressure 110 mm systolic and 70 diastolic.

The blood count revealed a leukocytosis of 10,400 with 62 per cent polymorphonuclears and 38 per cent lymphocytes. The Wassermann reactions on blood and spinal fluid, colloid gold curve and urine were negative. Chemical examination of the spinal fluid showed sugar 72 mg per cent and chlorides 650 mg. Roentgenography revealed clouding of the right ethmoid sinus, marked sclerosis of the antral cells of the right mastoid and moderate sclerosis of the left antral cells, increased convolutional markings of the skull, and a greatly flattened sella turcica. The clinoid processes were not visualized. The pineal body was calcified.

* Received for publication July 23, 1937.

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Course The course was characterized by marked variability of the neurological symptoms. Periods of mental clarity alternated with drowsiness, severe headaches and nuchal rigidity. Vomiting occurred infrequently and was never of the projectile type. The neurological signs also varied. Occasionally there was a suggestion of facial fixity. Scattered, unequal and variable reflexes were described. At times there were a questionable right Babinski and absent right abdominal reflexes. At times there was a definite palsy of the left side including the face and the patient was unable completely to close the left eye. An eye consultant found both discs hazy and the retinal vessels tortuous, especially on the left, indicative of a moderate degree of intracranial pressure probably more localized on the left side.



FIG 1 The cicatricial lesion of the left parieto-occipital cortex

Spinal taps always relieved the headache and drowsiness, sometimes very quickly. On the last day he became very restless and irrational and resembled a hypomania. Death occurred suddenly.

Spinal Fluid Findings Twenty-one spinal taps were performed. Only once was the fluid somewhat cloudy, on the other occasions it was water-clear. The pressures varied greatly, ranging from 3 to 4 mm Hg to 46 mm. Usually it lay between 26 and 38 mm. The cell counts were always increased, from 78 on admission, to 340. Lymphocytes predominated, 75 per cent or over. Globulin was always present in traces. Except in the first specimen, sugar was absent. Cultures and

animal inoculations remained negative throughout the entire duration of the disease. Fortunately portions of many of the fluids had been saved in the laboratory, and after the autopsy, the cultures and animal inoculations were repeated. The results were the same.

The temperature curve was of a remittent character, gradually rising from 99° to 102.6° in 10 days, then slowly falling to 98.4° by the middle of April. From then until the end, the fluctuations were greater, more septic in type and reached 103.6°. The pulse was relatively slow and closely paralleled the temperature.



FIG 2 The more compact lesion of the cerebrum showing the tuberculoid type of reaction. Torula are present within and outside the giant cells.

Necropsy The most prominent feature of the brain was the extreme edema and the enlargement of the right temporal lobe. In the cortex of the left parieto-occipital lobe was a small mass measuring 2 cm in diameter, densely hard in consistence and resembling a healed tuberculous lesion. Over the base of the cerebrum, pons and medulla, the meninges were finely granular.

On section, the most prominent lesion was found in the region of the basilar nuclei. The entire region appeared completely disorganized by minute necrotic bright yellow foci. The entire brain appeared engorged and edematous.

Histology Sections were taken from the basilar nuclei, parieto-occipital regions, pons, medulla, cerebellum, choroid plexus and gasserian ganglia

The lesion of the left parieto-occipital cortex was formed by a confluence of dense fibrotic masses with a concentric formation. Some of the masses contained fine calcium deposit. Others had small necrotic centers with numerous polynuclear cells and masses of chromatin. In one region there were torula, apparently undergoing degeneration and staining intensely by the gram technic. At the periphery of the lesion was a compact zone of lymphoid cells and a rare giant cell.

The most extensive lesions were in the regions of the basilar nuclei. They were lytic in nature and contained torula in very large numbers. These lesions

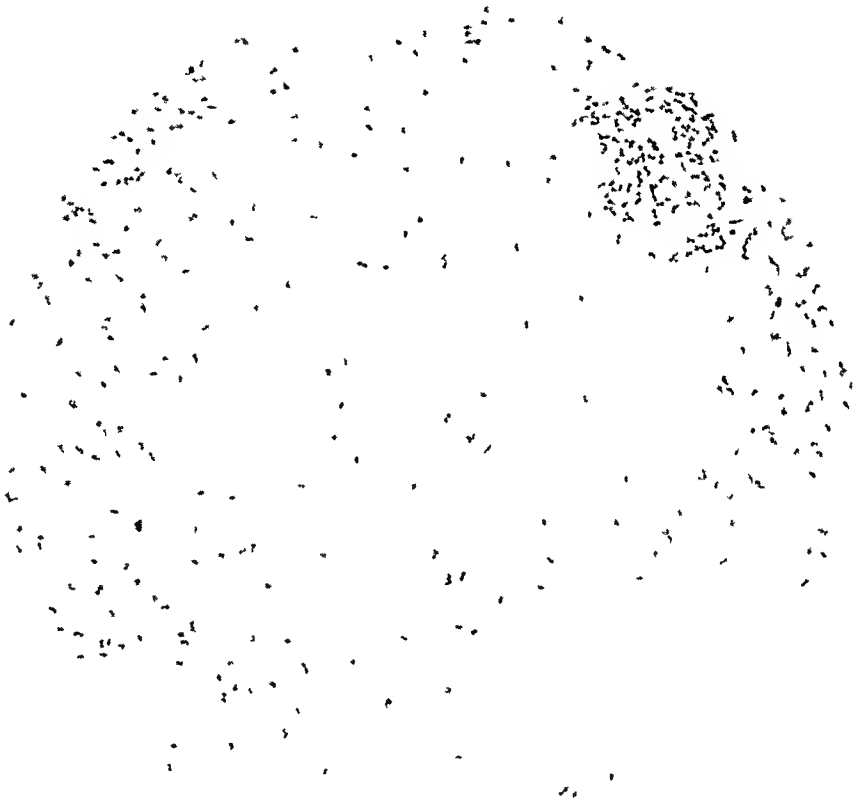


FIG 3 The more diffuse type of lesion, lytic in nature, showing the complete disorganization of the tissue. Section taken from the basilar ganglia

were not sharply delimited but involved the tissue diffusely. They merged into a more circumscribed lesion characterized by a tuberculoid reaction. Torula were present in these latter lesions both within and outside the giant cells.

The meningeal involvement was more intense over the pons and medulla than over the base of the brain. It was characterized by a tuberculoid reaction with numerous giant cells. The underlying tissue was involved by extension. Non-specific areas of degeneration with marked demyelination were prominent in the medulla.

The lesions of the choroid plexus and gasserian ganglia were similar to those of the meninges

Torula were present in profuse numbers, either free in the tissues or within giant cells. They were characterized by round, oval or egg shape, a single or double contour, frequently by spiked ends, and by budding. Staining reaction was variable. With hematoxylin and eosin, the capsules stained usually dark or light blue, sometimes with a narrow eosin-stained peripheral zone. With the gram stain, the heavier capsules stained intensely brown, the finer capsules red. The double contour frequently was much sharper with the gram stain than with hematoxylin.

Torula lesions of a tuberculoid nature were found histologically in the kidneys. All the other organs were negative.

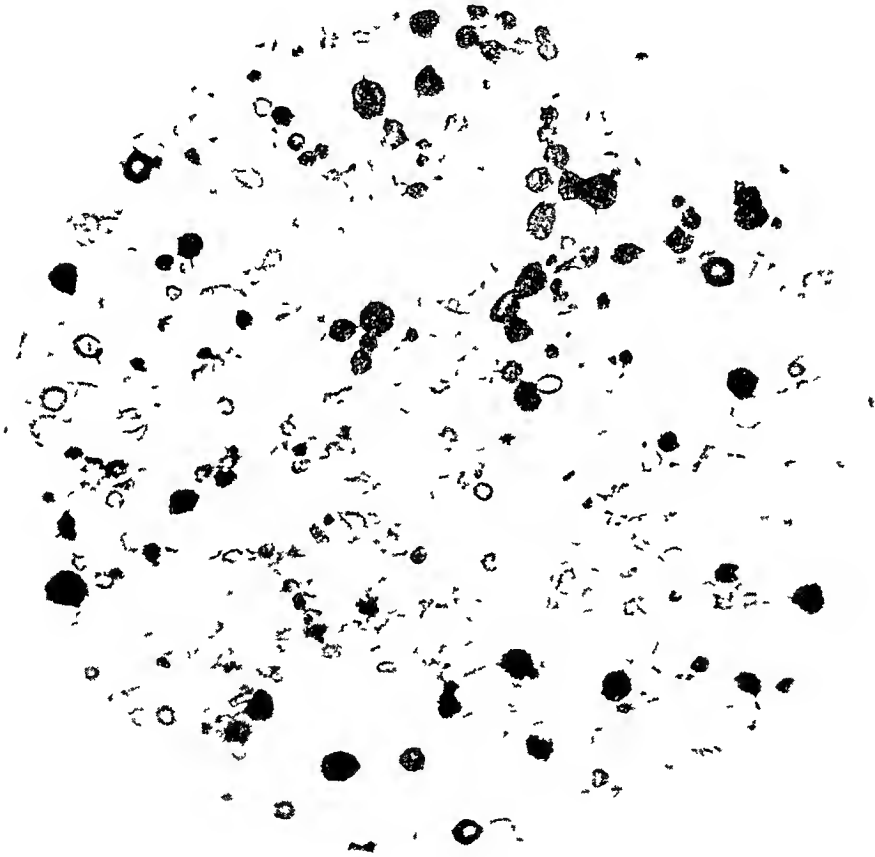


FIG 4 The same region as figure 3, stained by the gram technic. This view shows the profusion of the organisms, their shape, the variability of reaction to the stain, the spiked ends and the budding.

COMMENT

The rapid course, the fever and the history of tuberculosis of cervical lymph nodes suggested in this case the diagnosis of tuberculous meningitis. The repeatedly negative results of animal inoculations, however, was a strong point against this diagnosis. Because of them, the possibility of torulosis was en-

tertaind The negative bacteriological results again prevented a correct diagnosis being made The failure to demonstrate torula in the cerebrospinal fluid is unusual, since most cases are positive, at least late in the disease That the results were due to discarding the cultures too soon, a point mentioned by Levine, does not apply to this case, since they were kept for a period of one month The inoculated animals were kept for two months before killing The first positive evidence was offered by the histological examination The most acute and youngest lesion was in the meninges

The chronic cicatrizing lesion of the cortex has hitherto been unreported in the literature That this lesion is due to torula is proved by the presence of organisms The odd persistence of the organism has also been observed by Weidman³ in experimental torulosis in the monkey Lesions which had spontaneously regressed and been replaced by scar tissue, still had demonstrable organisms In the present case, the cicatrix appears to be the only explanation of the epileptiform seizures which had occurred over a four year period

The history of cervical adenitis diagnosed tuberculosis is a further point of interest Unfortunately no biopsy was performed, so definitive pathology in this gland could not be decided That it may have been torula infection is possible A mistake in diagnosis of a cervical adenitis was reported by Wile⁴ Although in his case, Hodgkin's disease had been diagnosed, subsequent examination revealed that the lesion was due to torulosis

SUMMARY

A case of torula meningo-encephalitis is reported There was a history of epileptiform seizures extending over a four year period and a final acute meningo-encephalitic syndrome of seven weeks' duration simulating tuberculosis The diagnosis of torula infection was made at the postmortem table The pathological changes revealed all stages of torula infection and included a cicatrizing brain lesion, a hitherto unreported observation

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EXANTHEM SUBITUM, REPORT OF A CASE

By MORGAN CUTTS, M D, *Providence, R I*

R C, a white female aged 31, was first seen on February 3, 1937, complaining of general malaise and weakness of one day's duration Three days previously she had returned from a week's trip to Texas, and had felt quite well until she noted chilly feelings, weakness, some headache and general malaise on February 2 She had no coryza, sore throat, aching in bones or joints, lachrimation, cough, or pain in

* Received for publication July 9, 1937

the chest, and she had taken no drugs of any kind recently. She had had both measles and rubella as a child, but not scarlet fever, and the remainder of her past history and family history was non-contributory.

On physical examination her temperature was found to be 102° by mouth, but apart from this there were no abnormal findings. Her throat appeared normal, and a throat culture was subsequently reported negative for hemolytic streptococci.

There were no Koplik spots, and no glandular enlargement. A leukocyte count done later the same day was 3,200 with approximately 50 per cent polymorphonuclears. It was remarked at the time that she was surprisingly free of symptoms, as the slight malaise she had complained of had been completely relieved by 32 mg of codein and 0.6 gm of aspirin. Her temperature remained elevated between 100° and 102° for three days, without the development of any other symptoms, after which it suddenly dropped to normal and there appeared at the same time a measles-like rash, in places confluent, over the neck, body, and upper arms. This in turn faded after 24 hours and had completely disappeared in two days. There was no subsequent rise in temperature, and the patient was discharged with a diagnosis of *exanthem subitum*. Several days after recovery her white blood cell count was found to be 7,600.

Zahorsky¹ first clearly described this disease in 1910 and 1913 under the name of *roseola infantum*, and Vieder and Hempelmann² in 1921 suggested the name of *exanthem subitum*.

A recent article by Zahorsky³ clearly describes the typical course of this disease in infants and children. One attack usually confers immunity, and only rare instances of infection of one child by another have been observed. The incubation period is believed to be 8 to 14 days. Fever lasts for approximately four days and falls suddenly, at which time the rash appears, first on the back and abdomen, and rapidly spreads to involve most of the body. Constitutional symptoms, such as restlessness, headache, and gastrointestinal disturbances, may be more or less marked, but are rarely severe. Leukopenia is a constant finding, and affects chiefly the cells of the granular series. No complications have been observed. No previous report of a case occurring in an adult could be found in the literature.

As in the case here reported measles, rubella, and scarlet fever can generally be ruled out fairly easily, especially by the typical time relationship of the fever and rash. The absence of any severe symptoms or of a second rise in fever also speaks against dengue, which was a definite possibility in this case, and is mentioned by Zahorsky as a possible source of error.

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A CASE OF CARCINOMA OF THE ISLANDS OF LANGERHANS WITH HYPOGLYCEMIA^{*}

By HENRY JOACHIM, M D, F A C P, and MORRIS M BANOWITCH, M D, F A C P, *Brooklyn, New York*

THE syndrome of spontaneous hypoglycemia described by Seale Harris¹ was attributed by him to hyperinsulinism. Since then this conception has been amply confirmed by numerous reports in the literature, and particularly demonstrated by Wilder, Allan, Power and Robertson² in 1927. They reported a case of carcinoma of the islands of Langerhans with liver and lymph node metastases, the extract of which was found capable of lowering the blood sugar in rabbits.

In the past 10 years numerous cases of spontaneous hypoglycemia due to tumor formation have been reported but the great majority have been due to hyperfunctioning of adenomas of the islands of Langerhans. Islet carcinoma causing this syndrome has been relatively rare. There have been seven cases (Wilder² et al., Hamdi³, Judd, Faust and Dixon⁴, Bickel, Mozer and Junet⁵, Cragg, Power and Lindem⁶, Howland, Campbell, Maltby and Robinson⁷, Graham and Womack⁸). To these we wish to add a case of spontaneous hypoglycemia due to islet carcinoma.

CASE REPORT

The patient was a female, aged 31, housewife by occupation, who was admitted to the Beth Moses Hospital April 4, 1935 and died May 27, 1935. The chief complaint on admission was of convulsions for the preceding three days, followed by coma eight hours prior to admission.

The family history was essentially negative except that one sister was suffering from encephalitis. Patient had given birth to five children, all living and well.

Eleven years before, following childbirth, she had developed salpingitis from which an uneventful recovery had taken place with no operative interference. Otherwise patient had never been ill.

For the past four years the menstrual periods had been somewhat irregular and she had noticed that her bleeding had increased.

The present illness began three days before admission when suddenly the patient began to sweat profusely. This was followed by convulsions which involved the entire body, and which were followed by comatose periods of varying duration. On awakening she would remember nothing. During the three day period she had numerous such attacks, the last attack commencing at 4 p m on the day of admission to the hospital, at 11 p m the patient was still in coma.

In checking back the history we received the following information. Four weeks prior to admission the patient had fallen down a flight of stairs and since that time had complained of headaches and had experienced several fainting spells.

On admission the patient was comatose. She was well nourished with some tendency towards obesity. There was no evidence of any cranial nerve palsies, no rigidity of the neck. The heart and lungs were essentially negative, the liver and spleen were not felt. After the patient had come out of coma, there was definite tenderness noted above her umbilicus and somewhat to the left, but no definite masses were palpated.

The temperature on admission was 99.8°, pulse 100, respiration 22. Blood pressure 130 systolic and 70 diastolic. Examination of the urine was negative. The

* Received for publication July 31, 1937.

blood sugar, taken immediately on admission and before the administration of glucose was 30 mg per 100 c c

A diagnosis of hypoglycemic shock secondary to hyperinsulinism, was made. At that time the possibility of adenoma of the pancreas as an underlying pathological factor was considered.

Intravenous administration of 50 per cent glucose brought the patient out of coma quickly.

For the next two days the patient had no attacks, but, on April 5, at 12 30 a m, she lapsed into coma. Intravenous glucose was given and the patient responded well. The third attack occurred on April 6, at 6 28 a m, the patient again passed into coma, intravenous glucose was given, but the response was not as dramatic as on the first administration. The blood sugar at this time was 25 mg per 100 c c. The patient remained in fairly good shape without any attacks until April 11. During this period she received glucose frequently by duodenal tube and in her diet. Her blood sugar remained at 70 mg. Another hypoglycemic attack occurred on April 12 during which her blood sugar fell to 25 mg.

On April 8 a glucose tolerance test was carried out. Specimens were taken every 15 minutes from 10 45 a m to 4 45 p m.

Sugar Tolerance Test

10 45 Blood sugar 120 mg	(100 grams of glucose were given)
11 05 Blood sugar 125 mg	1 10 Blood sugar 75 mg
11 20 Blood sugar 130 mg	1 30 Blood sugar 65 mg
11 35 Blood sugar 150 mg	2 00 Blood sugar 65 mg
11 50 Blood sugar 65 mg	3 15 Blood sugar 60 mg
12 05 Blood sugar 65 mg	3 45 Blood sugar 50 mg
12 15 Blood sugar 60 mg	4 15 Blood sugar 70 mg
12 30 Blood sugar 60 mg	4 45 Blood sugar 75 mg
12 50 Blood sugar 70 mg	

Because of the repeated attacks of coma the patient was transferred to the surgical service for operative interference. On April 15 exploratory laparotomy was performed by Dr. Harold Rabinowitz, and the findings were as follows:

The liver, gall-bladder, stomach and duodenum were normal. Along the lesser curvature of the stomach a hard indurated gland could be felt, the size of a pea. In the terminal half of the pancreas a hard irregular and nodular mass about the size of a tangerine orange and several large glands were palpated. The vessels of the spleen seemed to be buried in the mass at the tail end of the pancreas. The spleen had to be removed in order to get at the mass in the pancreas. Only part of the neoplasm could be removed. The patient's immediate postoperative reaction was good.

The pathological report was as follows:

Gross The specimen consists of a spleen and two small portions of pancreatic tissue. The spleen weighs 170 grams. It is moderately firm and rubbery in consistency and on cross section presents a homogenous reddish-brown appearance. The trabecular markings are distinct. The follicles are indistinct. The masses of pancreatic tissue reveal firm, discretely circumscribed, golden-yellow nodules, ranging from 3 to 7 mm in diameter. They are firm in consistency, and in the second portion of tissue removed reveal some degree of invasion of the surrounding normal lobules of pancreas, which are of a more grayish-tan color. In this portion of tissue, there is a discretely circumscribed structure, apparently a lymph node, measuring 7 cm in length, and 1 cm in diameter. Cross section reveals a pearly-gray appearance with a thin rim of lymphoid tissue surrounding the pearly-gray nodular mass. The portions of tissue removed are too small for biochemical assay.

Nests of polygonal cells with large clear nuclei are present. The latter have well-formed nuclear membranes and contain a nucleolus. The nuclei vary considerably from clear vesicular structures to large hyperchromatic nuclei with coarse



FIG 1 (*above*) Island cell carcinoma in the pancreas (low power)
FIG 2 (*below*) Island cell carcinoma in the pancreas (high power)

chromatin clumps. The nests are covered with a layer of syncytial-like cells. Aniline-fuchsin-methyl green stains reveal only a few green granules in the cytoplasm, whereas the islets in the normal portion of pancreas contain red and green granules. The cytoplasm is dust-like and contains numerous vesicular structures.

A lymph node contains nests of similar cells

The spleen reveals sinus hyperplasia and distention. The follicles are somewhat compressed. The sinus reticulum is hyperplastic.

Diagnosis Carcinoma of the pancreas with lymph node metastasis. Chronic passive congestion of the spleen.

For the first four days after operation glucose was administered frequently by duodenal tube and vein. The patient was free from attacks of coma. However, on April 19 another episode of sweating, convulsion and coma took place, and, from then on these attacks kept recurring daily so that on April 29 there were only traces of sugar in her blood. From then on the attacks of sweating and twitching recurred frequently in spite of almost continuous glucose administration. The glucose became less effective and the patient expired May 27.

Additional laboratory findings were: Wassermann and Kahn tests were negative. Her blood count on admission was: Hemoglobin 90 per cent, red blood count 4,100,000, white blood count 15,200, polynuclears 64 per cent, lymphocytes 36 per cent. Prior to her death blood count was as follows: Hemoglobin 50 per cent, red blood count 3,000,000, white blood count 40,000, polynuclears 85 per cent, lymphocytes 15 per cent.

The response to adrenalin injection was as follows:

10 42	Blood sugar	70 mg
10 45	10 minims of adrenalin was injected	
11 01	Blood sugar	60 mg
11 20	Blood sugar	55 mg
11 40	Blood sugar	60 mg
11 50	Blood sugar	55 mg
12 00	Blood sugar	45 mg

At this time patient was sweating, apathetic, twitching, and glucose had to be given.

A roentgenogram of the patient's skull revealed the presence of a definitely small sella turcica which was morphologically normal.

The urine was repeatedly negative, except on occasions when traces of sugar were found, probably as a consequence of the glucose injections.

DISCUSSION

Since the new era in the treatment of diabetes was initiated by the discovery of insulin, the more common use of blood sugar determinations has revealed the frequent presence of a diminution in the normal amount. The normal limits on a fasting stomach vary from 80 to 110 mg per 100 c c of blood, the limits depending upon the method used in the determination. Low blood sugar readings of 70 mg or less may depend upon an excess of insulin therapeutically administered or spontaneously secreted by the islets of Langerhans. For this latter type Seale Harris coined the name of hyperinsulinemia in 1924. Since then many cases of this condition have been observed. Wilder of the Mayo Clinic was the first in 1927 to establish the causal relationship of tumors of the islet cells, insulomas, to hypoglycemia due to hyperinsulinemia. There are other causes of hypoglycemia not dependent upon structural changes of the islets of Langerhans. From a clinical standpoint a persistent spontaneous hypoglycemia is still not generally recognized by the profession and hypoglycemic states masquerade under the picture of a multitude of diseases.

The normal blood sugar is the balance resulting from the liberation of stored glycogen from the liver into the blood stream as glucose, and the withdrawal of some of this glucose from the blood for tissue deposit and utilization. The difference between the arterial and venous blood sugar is equivalent to that abstracted from the blood for tissue storage or consumption.

Hypoglycemia is present in starvation and states of inanition caused by malignancy, in prolonged fever, excessive vomiting, diarrhea, celiac disease, sprue, extensive hepatic damage, prolonged muscular activity as in forced military marches, Addison's disease, other states of hypoadrenia as after extensive burns, adrenal hemorrhages or toxic adrenal depression as from diphtheria or sepsis, in cases of myxedema, progressive muscular atrophy and myasthenia gravis. In pituitary hypofunction (Simmonds disease) the blood sugar may be extremely low. New-born infants delivered from diabetic mothers may suffer from hypoglycemia as a result of a prenatal compensatory islet hyperplasia to supply the necessary maternal insulin. Hypoglycemia is a characteristic feature of von Gierke's disease.

In discussing the symptoms we are not taking into consideration the acute hypoglycemic states induced by the administration of excessive doses of insulin. We are at present concerned with chronic spontaneous hypoglycemic states.

The most frequent symptom is fatigue and easy exhaustibility, often dissipated by a meal rich in carbohydrates. Extreme hunger, absence of satiation and a constant feeling of emptiness, with a sinking sensation, vertigo, irritability and an excitability resembling that of alcoholism have been observed. Nausea and vomiting may occur. Tremors are often present. The pulse may be rapid and the blood pressure may be low though it is sometimes elevated. Convulsive seizures, diplopia, transient attacks of aphasia and hemiplegia may be due to hypoglycemic states. Hyperhidrosis may occur. Some patients complain of a constant chilliness. Insomnia is a frequent symptom. The first evidence of hypoglycemia may be coma. Attacks of angina pectoris may be precipitated by hypoglycemia. The basal metabolism is low.

SUMMARY AND CONCLUSIONS

A case of spontaneous hypoglycemia is reported in which the entire syndrome ran its course in two months. At operation a tumor of the pancreas which proved to be a carcinoma of the islets of Langerhans was found. There were numerous lymph node metastases, and as far as could be determined no metastases of the liver were present. No autopsy was obtained. There were no attempts to demonstrate the presence of insulin in the tumor tissue. However, in view of the cases reported by Wilder et al. and Cragg et al., we believe that we are justified in classifying this case as one due to true hyperinsulinism.

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EDITORIAL

ADVANCES IN THE TREATMENT OF PELLAGRA

THE success of Goldberger and his associates in experimentally producing pellagra in man and its counterpart, black tongue, in dogs proved that a dietary deficiency plays an essential part in the production of these diseases. His demonstration that yeast, liver, and other foods rich in vitamin B₂ (G) prevents and usually cures the disease indicates that the active substance is probably to be found in some portion of the vitamin B₂ complex.

Certain facts, however, have led some investigators to believe that other factors are also concerned in the development of the disease. It seems probable that some individual predisposition must exist. The disease, at least in its outspoken forms, appears only in a relatively small portion of a community whose diet seems significantly deficient. Furthermore, a patient with outspoken pellagra may recover without specific treatment while on a diet like that of Goldberger, which is markedly deficient in B₂ although it does not lack this entirely. Thus in a series of 107 cases of pellagra reported by Ruffin and Smith,¹ 30 recovered completely while on such a diet before any treatment was given.

The suggestion has been made that there is a lack of some intrinsic factor also in susceptible individuals. Thus Sydenstricker and Thomas² believe that there is a deficiency of gastric secretion analogous to, but different from, that found in pernicious anemia. They reported lasting improvement in several patients who were kept on a deficient diet and treated only by the administration of normal gastric juice, and suggested that the effectiveness of the latter was due to the fact that it made possible the efficient utilization of the small amounts of "extrinsic factor" (in the B₂ complex) present in the diet.

The injurious effect of exposure to sunlight has also been emphasized.³ There is no doubt that sunlight may precipitate an attack of pellagra and aggravate the dermatitis, and that it may cause a relapse in inadequately treated patients. However, sunlight alone will not cause the disease, nor will protection from exposure always prevent its development.

The observations of Goldberger justified the hope that relatively simple dietary measures would prove effective in both preventing and curing the disease. Thus far, however, the results obtained are rather disappointing. Although the incidence of pellagra in the United States has diminished, it is still far too prevalent, as is indicated by the mortality rate of over 3000 deaths annually, reported to the United States Public Health Service. Fur-

¹ RUFFIN, J. M., and SMITH, D. T. A clinical evaluation of the potency of various extracts of liver in the treatment of pellagra, *South Med Jr*, 1937, **xxx**, 4-14.

² SYDENSTRICKER, V. P., and THOMAS, J. W. Some factors in the etiology of pellagra, *South Med Jr*, 1937, **xxx**, 14-18.

³ SMITH, D. T., and RUFFIN, J. M. Effect of sunlight on clinical manifestations of pellagra, *Arch Int Med*, 1937, **lix**, 631-645.

thermore, the therapeutic procedures which have been generally employed have not proved successful in the severer cases. Thus Spies, Chinn and McLester⁴ reported an average mortality rate of 32 per cent in the Hillman Hospital in Birmingham, Alabama. These unsatisfactory results, however, were probably due in part to inadequate treatment. These investigators were able to reduce the mortality rate in a series of 73 cases of endemic pellagra to 7 per cent by giving larger quantities of food and much larger doses of yeast and liver, provided a sufficient staff of nurses was available to insure that the quantities prescribed were actually consumed.

The effectiveness of liver in the treatment of pellagra has led to the investigation of the therapeutic activity of various types of liver extracts. One of the most careful studies is that of Ruffin and Smith,¹ based on 77 cases who failed to improve while on the basic (deficient) diet. They found that a relatively crude unconcentrated extract for oral administration in pernicious anemia (Valentine's, N N R) was highly potent in curing pellagra, but that the use of concentrated extracts by parenteral channels was definitely less satisfactory. Following the administration of large doses at frequent intervals, in most cases the stomatitis subsided within a few days, and some general improvement followed. Usually, however, either recovery was only partial, or relapse followed quickly after exposure to sunlight. If the oral extract was fractionated by the addition of alcohol, neither the filtrate (which contains most of the pernicious anemia principle) nor the precipitate, if administered individually, gave satisfactory results. The administration of both simultaneously, however, was highly effective. This observation, if confirmed, would indicate that two substances are concerned.

The substance or substances which are required to prevent pellagra are not yet definitely known. Several substances with different physiological properties have been isolated from the vitamin B₂ complex. Of these the best known is riboflavin (lactoflavin), a fluorescent dye which plays an important part in the oxidation-reduction reactions in all the body cells. Although a deficiency of this substance causes disease in rats, symptoms due to a deficiency in man have not been recognized, and its administration does not cure pellagra. The same appears to be true of the fraction vitamin B₆, lack of which causes a dermatitis in rats, and probably of the "filtrate factor."⁵

In September 1937, Elvehjem et al.⁶ reported the isolation of nicotinic acid amide from liver extracts which were effective in curing black tongue in dogs. They found that this substance, as well as commercial preparations

⁴ SPIES, T. D., CHINN, A., and McLESTER, J. B. Treatment of endemic pellagra, *South Med. J.*, 1937, **XXX**, 18-21.

⁵ JUKES, T. H., and LEPKOVSKY, S. Distribution of "filtrate factor" (water soluble vitamin belonging to vitamin B complex and preventing dietary dermatitis in chicks) in certain feedings, *Jr. Biol. Chem.*, 1936, **CXLIV**, 117-121.

⁶ ELVEHJEM, C. A., MADDEN, R. J., STRONG, F. M., and WOOLEY, D. W. Relation of nicotinic acid and nicotinic acid amide to canine black tongue, *Jr. Am. Chem. Soc.*, 1937, **lix**, 1767.

of nicotinic acid, promptly cured the black tongue. This observation led at once to the trial of nicotinic acid in the treatment of human pellagra, and several reports as to its effectiveness are already available. Spies, Cooper and Blankenhorn⁷ in November 1937, reported the successful treatment of several cases, and recently⁸ have reported the results obtained in 11 cases in all. These investigators (as a rule) kept their patients for one to three days on a deficient basic diet, to exclude a spontaneous improvement, and then treated them with nicotinic acid for one to three days. Subsidence of the glossitis and stomatitis was utilized as evidence of the effectiveness of the treatment, and this was manifested dramatically in every case within 24 to 72 hours. Most of the patients, because of the severity of their illness, were then also given the usual routine treatment for pellagra, so that their observations do not prove how effective nicotinic acid alone would be in curing the other manifestations of the disease. However, Smith, Ruffin and Smith⁹ have reported one case, and Fouts et al.¹⁰ have reported four cases of pellagra who were kept on a deficient diet and treated with nicotinic acid alone. Recovery in all cases appeared to be complete and as satisfactory as that obtained with liver extract, except that the dermatitis subsided more slowly.

The dose of nicotinic acid and the mode of administration varied greatly, and within limits appeared to be immaterial. From 0.15 to 1.0 Gm was given by mouth daily in divided doses, or in some cases from 30 to 60 mg intravenously or from 50 to 100 mg by hypodermoclysis. The larger doses caused transient sensations of heat, flushing and tingling of the skin, but no untoward reactions were noted.

The exact relation of nicotinic acid to pellagra has not yet been established, but the evidence strongly suggests that it may prove to be the pellagra-preventive factor of Goldberger. It seems certain to prove a very valuable aid in the treatment of the disease, particularly in the severe cases. Until its effectiveness and its limitations have been more precisely determined, it should be used with due caution, and as a supplement, rather than a substitute for the usual measures of treatment. The cheapness of nicotinic acid would also make practicable its use as a prophylactic measure, if further study shows that it is safe and effective for this purpose.

P C

⁷ SPIES, T. D., COOPER, C., and BLANKENHORN, M. A. Central Society for Clinical Research, Chicago, Nov. 5, 1937.

⁸ SPIES, T. D., COOPER, C. and BLANKENHORN, M. A. Nicotinic acid in the treatment of pellagra, Jr. Am. Med. Assoc., 1938, cx, 622-627.

⁹ SMITH, D. T., RUFFIN, J. M., and SMITH, S. G. Pellagra successfully treated with nicotinic acid: a case report, Jr. Am. Med. Assoc., 1937, cx, 2054-2055.

¹⁰ FOUTS, F. J., HELMER, O. M., LEPKOVSKY, S., and JUKES, T. H. Treatment of human pellagra with nicotinic acid, Proc. Soc. Exper. Biol. and Med., 1937, xlvii, 405.

REVIEWS

The Practitioner's Library of Medicine and Surgery Supervising Editor, GEORGE BLUMER, M A (Yale), M D, F A C P, David P Smith Clinical Professor of Medicine, Yale University School of Medicine, Consulting Physician to the New Haven Hospital *Supplement and Index Volume* xlv + 1161 pages, 177 illustrations D Appleton-Century Company, Inc, New York 1938 Price, \$10 a volume

The unnumbered *Supplement and Index* volume, which completes *The Practitioner's Library of Medicine and Surgery*, is the thirteenth in the series. The first of these was given notice in the ANNALS in 1932, and a brief description of each of the succeeding volumes has appeared in these columns. In the present volume the supplemental section comprises 808 pages, and to it 67 authors have contributed. In general, the topics have been arranged in the order of presentation in the preceding volumes with subdivision into sections accordingly. The material presented consists in part of a fuller or modernized treatment of topics already included in earlier volumes. The excellent chapter on The Symptoms, Diagnosis and Treatment of Trichinosis is illustrative of this group. It is a much needed addition to the overly compressed discussion of this subject in Volume III. To a considerable degree the Supplement deals with newer disease concepts, some of which will be found presented here in textbook form for the first time. Meloidosis, Rift Valley fever, onchocerciasis, radium poisoning, calcinosis, glycogenosis, regional ileitis, liver deaths in surgery and the Laurence-Moon-Biedl syndrome are examples of newly defined or recently restudied diseases which are discussed authoritatively. Other important chapters deal with the newer work on the ductless glands and sex hormones, blood chemistry, Boeck's sarcoid, drug reactions, staphylococcic food poisoning, hypoglycemia, pulmonary carcinoma, various hereditary dysplasias, protamine insulin, artificial fever therapy, sympathectomy for vascular disease, sexual impotence in men and the psychological aspects of pediatric practice. To the practitioner with a keen interest in the newer developments in the entire field of Medicine, this volume will prove the most interesting and valuable of the series. The general index, which follows the new textual material, extends over 350 pages. It is not simply a combination of the individual volume indexes but a new compilation, which has made possible a full and logical division of each topic. The reviewer has tested it in various respects and it appears to be unusually adequate. To the supervising editor and his assistants, congratulations are due for the successful completion of the *Library*. It has been a huge task. With the success of the present Supplement in mind, we hope that other supplemental volumes will be forthcoming in order that the *Library* may be kept continuously abreast of the most advanced medical thought of proved value.

C V W

Diseases of the Skin By FRANK CROZER KNOWLES, M D Third Edition, thoroughly revised 640 pages, 16 X 24 cm Lea and Febiger, Philadelphia 1935 Price, \$6 50

The author has presented a text whose chief value both to the student and to the practitioner of medicine lies in the excellent clinical descriptions presented of cutaneous diseases, and of those systemic diseases which have cutaneous manifestations. Dr Knowles has made every attempt to present in a concise manner, in simple

language, a word picture of skin diseases that can be readily understood. He has devoted one chapter to the subject of diagnosis, in which in semi-tabular form he has listed the sites of predilection, and configuration of the commoner skin diseases. The chapter on therapy is an excellent guide in prescribing treatment for patients, radium, roentgen-ray and actino-therapy are all discussed briefly but clearly. The reader is made to feel that dermatology is not a thing apart but that it is an integral part of medicine.

H. M. R., JR.

Clinical Laboratory Diagnoses. By SAMUEL A. LEVINSON, M.S., M.D., and ROBERT P. MACFATE, Ch.E., M.S. 877 pages, 14.5 × 23.5 cm. Lea and Febiger, Philadelphia. 1937. Price, \$9.50.

The authors have reviewed the pertinent subject matter of anatomy, physiology, biochemistry and pathology at the beginning of each main division of clinical pathology. Such treatment is of necessity too brief and incomplete to be of value for reference though of aid to the student in review. The occasional brief comments on methods of treatment might better have been omitted.

In addition to comprehensive sections on the analysis of gastric and duodenal contents, feces, urine, sputum, blood chemistry, hematology, immunology and serology, spinal fluid, general bacteriological procedures, histological technic, and the metabolism test there are chapters not often included in similar volumes. These unique sections deal with the laboratory methods in pediatric procedures, legal medicine and toxicology, skin tests and biological tests and a 59-page appendix dealing with the conduct of a course in clinical pathology. This appendix is of value to those interested in teaching the subject.

Few clinical pathology textbooks include such a wide variety of material pertaining to the laboratory. There are very few omissions of important material—the technic for the detection of Bence-Jones protein in the urine being one.

J. H. M.

Manual of Psychiatry and Mental Hygiene. By AARON J. ROSANOFF, M.D., University of Southern California. 1091 pages. John Wiley & Sons, New York. 1938. Price, \$7.50.

This seventh revised edition is one of the first books on psychiatry to come off the press in 1938, and is surprisingly up-to-date. Recent research in this specialty is presented, and generally accepted views are synthesized into a working manual of diagnosis, prevention, and treatment. The case method is used to clarify each subject discussed.

The volume is divided into six parts. Part I presents the neuropsychiatric syndromes and their etiology. Part II presents in detail the individual pathological conditions found. Part III is devoted primarily to therapeutics, and Part IV to prevention or mental hygiene. Part V gives the various special diagnostic procedures that need to be referred to continually in psychiatric practice, and Part VI gives several supplementary aids, which make the volume complete as a reference book.

This book has stood the test of time, and in this rewritten form the internist will find much valuable advice that he is constantly being called on for. Psychiatry has made many developments during the past ten years, and Rosanoff appears to have missed nothing.

J. L. McC.

A Method of Anatomy By J C BOILEAU GRANT, Professor of Anatomy in the University of Toronto lxvii + 650 pages William Wood & Co, Baltimore 1937 Price, \$6 00

There are no textbooks of human anatomy in English which combine adequate descriptive treatment with a clear explanation of mechanical function. All contain details which should enable an experienced anatomist to deduce the functional design of a given part or region, but the treatment is mainly concerned with a description of systemic anatomy, functional analysis of the whole organ or region being confined to generalities in small print. The so-called "applied anatomies" do not meet this need, for they are primarily designed to introduce the surgical approach. For the architectonic principle of structure one must turn to the works of Fick and Braus, which unfortunately are not available in translation.

Professor Grant has perceived this divergence in the modern development of anatomy and has sought to restore the attitude which became prevalent with Borelli's *De motu animalium*. His 'method' is essentially that of regional anatomy as exemplified in a good dissecting manual with the difference that it goes on to clarify the region in terms of functional adjustments. Wherever comparative and developmental anatomy can serve to establish a particular line of evidence they are aptly drawn upon.

The treatment of the acromio-clavicular joint may be quoted in part to illustrate the application of the deductive principle. "The *conoid* and *trapezoid ligaments*, into which the *coraco-clavicular ligment* is subdivided, resist such a force [a fall on, or a blow applied to, the edge of the acromion], it is their duty to hold the scapula laterally and to prevent it from being driven medially. If this be true, their fibers must obviously pass medially and downwards which they do. If they are to retain the scapula in position they could obviously take no other direction."

The section on the abdomen, especially with regard to the peritoneal relations of the viscera, is the most comprehensible to be found in an English text. The *situs viscerum* is presented with a clear account of the developmental events leading up to it in a manner quite similar to that of Braus in *Anatomie des Menschen*.

There are 564 line drawings which drive home the deductive principles of the text in a peculiarly forceful way. They make no pretense of being rigidly factual, they serve rather the function of the lecturer's blackboard diagram.

The system of nomenclature used is the Birmingham Revision of B N A with the standard B N A equivalents usually given in parentheses. Whether this feature is an advantage or a defect from the point of view of American anatomy remains for the future to say.

On the whole the book is to be highly recommended for teachers and students alike. It can not be considered in any way to supplant the standard reference texts, but can be used with them as a valuable adjunct to acquiring a conception of the human organism as a whole.

J C L

The Colon as a Health Regulator—From a Surgeon's Point of View By SIR HENRY M W GRAY, K B E, C M G, L L D (Aberdeen), M B, C M (Aberdeen), F R C S (Edinburgh) 100 pages, 13 × 20 cm The Macmillan Company of Canada, Ltd, Toronto 1936 Price, \$2 50

The author subscribes to and enlarges upon the thesis that colonic stasis, stagnation and putrefaction, the consequence of bands, kinks, adhesions and other abnormalities are frequent causes of vague abdominal symptoms and chronic ill-health.

Many patients, so ailing but giving none of the manifestations of the more obvious abdominal diseases, are in reality suffering from definite organic lesions, the presence of which most surgeons do not suspect, much less operate upon. Gray accepts in part the speculations of Lane but advances the hypothesis that most if not all kinks and adhesions are developmental abnormalities, the result of faulty descent of the cecum with irregular and imperfect fixations of the large gut. Cause and effect were confused by the older theorist.

The symptoms are many and varied, ranging from constipation, abdominal pain, nausea and vomiting to loss of weight, anemia, acneiform eruptions, nervous and "rheumatic" manifestations. The diagnosis is arrived at by the elicitation of some quite unusual and unorthodox physical signs.

The correction of the condition is accomplished by means of an unusual operation termed a "spring-cleaning" which combines the releasing of kinks and adhesions with the fixation of abnormally mobile portions of the large gut through a long laparotomy incision, done according to the author's formula. Justification for and recommendation of this operation form the main theme of the monograph.

Difficulty in preoperative recognition and selection of suitable cases may cast some doubt upon the desirability of routine adoption of such a procedure. Although there is a very low mortality rate and evidence of some immediate benefit, more convincing proof of its efficacy could be arrived at by a long follow-up of cases, which is not supplied.

M E

COLLEGE NEWS NOTES

GIFTS TO THE COLLEGE LIBRARY

Grateful acknowledgment is made of the receipt of the following donations to the College Library of publications by members

Books

- Dr Jacob Gutman (Fellow), Brooklyn, N Y—1st Second Series, Supplement to "Modern Drug Encyclopedia",
Dr Johannes M Nielsen (Fellow), Los Angeles, Calif—"Agnosia, Apraxia, Aphasia",
Dr David Riesman (Fellow), Philadelphia, Pa—"High Blood Pressure and Longevity and Other Essays",
Dr T H Shastid (Fellow), Duluth, Minn—"Light, The Raw Material of Vision"

Reprints

- Dr Victor W Bergstrom (Fellow), Binghamton, N Y—1 reprint,
Dr Oscar Costa-Mandry (Fellow), Santurce, P R—2 reprints,
Dr A Morris Ginsberg (Fellow), Kansas City, Mo—3 reprints,
Dr John L Goforth (Fellow), Dallas, Tex—1 reprint,
Dr Maurice Kovnat (Fellow), Staten Island, N Y—1 reprint,
Dr Johannes M Nielsen (Fellow), Los Angeles, Calif—19 reprints,
Dr William H Ordway (Fellow), Mount McGregor, N Y—4 reprints,
Dr Ellen C Potter (Fellow), Trenton, N J—1 reprint,
Dr Harold W Potter (Fellow), Newport News, Va—2 reprints,
Dr John C Ruddock (Fellow), Los Angeles, Calif—1 reprint,
Dr Osborne A Brines (Associate), Detroit, Mich—4 reprints,
Dr Lucien Y Dyrenforth (Associate), Jacksonville, Fla—2 reprints, 1 journal,
Dr Marcos Fernan-Nunez (Associate), Milwaukee, Wis—1 reprint,
Dr Hyman I Goldstein (Associate), Camden, N J—3 reprints,
Dr Donald E Griggs (Associate), Los Angeles, Calif—4 reprints,
Dr Enrique Koppisch (Associate), San Juan, P R—1 reprint,
Dr Charles E Lyght (Associate), Northfield, Minn—2 reprints,
Dr Abraham S Rubnitz (Associate), Omaha, Nebr—5 reprints,
Dr Frederick W Williams (Associate), New York, N Y—1 reprint

Acknowledgment is also made of the receipt of a copy of the new "Navy Directory," January 1, 1938, from the Bureau of Medicine and Surgery, and of a reprint, "A Portrait Gallery of Physicians—The Collection in the Army Medical Library," by Col Harold Wellington Jones (MC), U S A

Acknowledgment is also made of a gift to the College Library of a book of poems by Emilie Conklin, Indianapolis, Ind, entitled, "Doctors, I Salute!"

NEW LIFE MEMBERS

The following Fellows have been entered, upon their subscriptions, as Life Members of the American College of Physicians, at the dates indicated, making a total of ninety-eight

Dr Charles Ricksher, Norwich, Conn , February 1, 1938
Dr Floyd H Lashmet, Petoskey, Mich , February 11, 1938
Dr John Paul Ritchey, Missoula, Mont , February 14, 1938
Dr James F Churchill, San Diego, Calif , February 14, 1938

COMMITTEE ON GRADUATE EDUCATION AND INTERNAL MEDICINE

In accordance with directions embodied in the following resolution of the Board of Regents, December 12, 1937, Dr J H Means, President, has appointed the following Committee

"Resolved, that the Board of Regents authorize the appointment of a committee by the President of a size which he may select, not necessarily confined to members of the Board of Regents, but to be designated as a committee of the Regents, on the whole question of graduate education and internal medicine"

Dr William J Kerr, San Francisco, Chairman
Dr Charles H Cocke, Asheville
Dr Hugh J Morgan, Nashville
Dr Charles S Burwell, Boston
Dr Joseph A Capps, Chicago

It is intended that this committee shall supervise graduate courses in medicine arranged by the College for its members, and that the committee will also collaborate with other national committees, when and if its advice and assistance may be called for

CHARLES GODWIN JENNINGS MEMORIAL LECTURE

The FIRST ANNUAL CHARLES GODWIN JENNINGS MEMORIAL LECTURE was held January 27, 1938, under the auspices of the Staff of the Charles Godwin Jennings Hospital Following dinner at the Detroit Club, Dr A F Jennings (Fellow), President of the Board of Trustees and of the Medical Staff, presided at the meeting Brief addresses in memory of Dr C G Jennings (Master, deceased) were given by Dr H R Carstens (Fellow), Mr James Turner, Trustee of the Hospital, and Dr L J Hirschman (F A C S), who introduced the speaker of the evening, Dr Walter C Alvarez (Fellow) of Rochester, Minn Dr Alvarez delivered an address on "Origins of Modern Medicine"

REGIONAL MEETING OF KENTUCKY MEMBERS

About fifty Fellows and Associates of the American College of Physicians resident in Kentucky held their annual meeting and dinner in Louisville under the Governorship of Dr C W Dowden, February 16, 1938 Dr J Murray Kinsman was in charge of arrangements The following program was given at the Louisville City Hospital "The Insulin Treatment of Dementia Praecox," Spafford Ackerly, "The Diagnostic and Therapeutic Uses of the Bronchoscope," Maurice Buckles, "The Gastroscope as a Diagnostic Agent in Diseases of the Stomach," Sam Overstreet, "Demonstration of the Photo-Electric Colorimeter," John Walker Moore, "The Dying Heart," Virgil Simpson

In the evening a dinner meeting was held at the Pendennis Club, at which Dr James H Means, President of the College, was the guest of honor

Dr R A Hare (Fellow), formerly of the Staff of the Santa Barbara Cottage Hospital, Santa Barbara, Calif, has been appointed Medical Director of the Washington Sanitarium and Hospital, Washington, D C

Dr August A Werner (Fellow), St Louis, addressed the Sioux Valley Medical Association, Sioux Falls, S D, January 18, on "Anterior Pituitary-Gonad Relationship in the Female"

Dr Louis F Bishop, Jr (Fellow), New York City, addressed the Rutgers Medical Club January 27 at New Brunswick, N J, on "Coronary Artery Disease"

Dr William D Weis (Fellow), Crown Point, Ind, has been reappointed county health commissioner of Lake County, Indiana, for four years He is the only full-time county health commissioner in that State

Dr J C Geiger (Fellow), Director of Public Health of the City and County of San Francisco, has been granted the decoration, "Cruz de Caballero de la Orden del Merito," by the Government of Chile, for his "good friendship and assistance to that country and for his excellent work in and outstanding contributions to public health"

At a Gastro-Enterologic Symposium held by the Northern Medical Association of Philadelphia (Pa), January 17, Dr Anthony Bassler (Fellow), New York, presented a paper on "Etiology, Symptomatology, and Medical Treatment", Dr Henry A Rafsky (Fellow), New York, on "The Relation of the Anemias and Blood Dyscrasias to Disorders of the Gastrointestinal Tract in Adults" Dr T Grier Miller (Fellow), Philadelphia, was the commentator

Dr Robert M Moore (Fellow), Indianapolis, Ind, was elected President of the Indianapolis Medical Society for the year 1938, at its meeting December 7, 1937

Dr Philip I Nash (Fellow), Brooklyn, has been made President-Elect of the Kings County (N Y) Medical Society

Dr Carl Mundy (Fellow), Toledo, Ohio, has been honored by being elected the President-Elect of the Academy of Medicine of Toledo and Lucas County Dr Mundy will serve as President-Elect for 1938 and will assume the Presidency in 1939 He is also Chairman of the Advisory Board of Health for Toledo, which board counsels with the City Manager and the City Director of Health in matters of local health policy and health administration In addition to these activities, Dr Mundy is Director of Medicine at Lucas County Hospital

At the Thirty-Fourth Annual Congress on Medical Education and Licensure held in Chicago February 14 and 15, the following Fellows of the College participated
Dr Willard C Rappleye, Dean of Columbia University College of Physicians and Surgeons and President of the Advisory Board for Medical Specialties, "The Functions of the Special Examining Boards",

- Dr Burrell O Raulston, Professor of Medicine, University of Southern California School of Medicine, Los Angeles, "An Introduction to Clinical Medicine and Some Variations in the Curriculum of the Third and Fourth Years in Medical School",
- Dr J G FitzGerald, Director of the School of Hygiene and Connaught Laboratories, University of Toronto, "Undergraduate Instruction in Preventive Medicine",
- Dr J H Musser, Professor of Medicine, Tulane University School of Medicine, New Orleans, "Graduate Medical Education for the Internist",
- Dr James D Bruce, Director of the Department of Postgraduate Medicine of the University of Michigan, Ann Arbor, "Continuing Professional Education"
-

Dr Hyman I Goldstein (Associate), Camden, N J, was elected Vice President of the Northern Medical Association of Philadelphia (founded in 1846) for 1938 Dr Goldstein was also elected a corresponding member of the Hungarian Dermatologic Association, Budapest, Hungary, as recently confirmed by the Royal Minister of Internal Affairs of the Hungarian Government

The cornerstone of the new diagnostic clinic at the Boston Dispensary, Boston, Mass, was laid during December and dedicated to Dr Joseph H Pratt (Fellow), Professor of Clinical Medicine at Tufts College Medical School The building is to be known as the Joseph H Pratt Diagnostic Hospital The cornerstone was laid on Dr Pratt's sixty-fifth birthday The building was made possible by recent gifts of William Bingham, 2d, because of his interest in providing a medical center at which the development of rural medicine may be planned and supervised

Dr Anton J Carlson (Fellow), Professor of Physiology in the University of Chicago, is a member of the editorial committee of the "Annual Review of Physiology," in which it is proposed to review developments of each year or biennium in the major fields of physiologic research

A recent announcement by the Advisory Board for Medical Specialties states that a Commission on Graduate Medical Education has been created "to mobilize current opinion as to how the problems in this field can best be solved and to formulate the educational principles involved in graduate medical training" The president of the board, Dr Willard C Rappleye (Fellow), New York City, appointed four members of the board to form the Commission Among members of the Commission are the following Fellows Dr James D Bruce, Ann Arbor, Dr Anton J Carlson, Chicago, Dr Reginald Fitz, Boston, Dr Willard C Rappleye, New York, Dr Harold L Rypins, Albany, Dr Alfred Stengel (Master), Philadelphia, and Dr John B Youmans, Nashville

Dr Waller Smith Leathers (Fellow), Dean of Vanderbilt University School of Medicine, Nashville, Tenn, was selected as the speaker on medical education before a series of educational symposiums, which marked the formal inauguration exercises of Rufus Carrollton Harris, LL D, as the tenth president of Tulane University of Louisiana, New Orleans, during January Dr C C Bass (Fellow), Dean of the medical school at Tulane, presided

A library on tuberculosis, named in honor of the late Dr Luther F Warren (Fellow, deceased), was dedicated recently at a memorial service held for Dr Warren at the Brooklyn Home for Consumptives, of which Dr Warren was the medical director from 1932 until his death during January, 1937. Dr Warren was for a number of years very active in the American College of Physicians, being the Governor of the College for eastern New York and later a member of the Board of Regents and of the Committee on Credentials. He was Professor of Medicine at Long Island College of Medicine and Physician-in-Chief to the Long Island College Hospital.

Dr Asher Yaguda (Fellow), Newark, N J, has been elected President of the newly organized New Jersey Society of Clinical Pathologists.

Dr Fred M Smith (Fellow and Governor of the College for Iowa), Professor of the Theory and Practice of Medicine in the State University of Iowa College of Medicine, Iowa City, has been appointed the new Editor of the *American Heart Journal*, succeeding Dr Lewis A Conner (Fellow), Professor of Clinical Medicine at Cornell University Medical College, New York, who has retired. Among the new associate editors is Dr Irving S Wright (Fellow) of New York City.

Dr Russell S Anderson (Associate), until recently a member of the staff of the Michigan State Sanatorium, Howell, Mich, has been appointed Superintendent of a new hospital for the treatment of tuberculosis in Erie County, near Erie, Pa.

In connection with a three-day ceremony marking the inauguration of Oliver C Carmichael, LL D, as Dean of the Graduate School and Senior College of Vanderbilt University, Nashville, Tenn, the following Fellows participated in the symposium devoted to Medicine:

- Dr William D Cutter (Fellow), Secretary, Council on Medical Education and Hospitals, American Medical Association, "Trends in Premedical and Medical Education",
 - Dr Thomas Parran (Fellow), Surgeon General of the U S Public Health Service, Washington, D C, "A Forward Look at National Health",
 - Dr Wilburt C Davison (Fellow), Dean of Duke University School of Medicine, Durham, N C, "A Survey of Medical Education in the South"
-

Dr Ernest E Irons (Fellow), Clinical Professor of Medicine and formerly Dean, Rush Medical College, Chicago, delivered a public lecture on "The Problem of Arthritis and Its Causes" at the Goodman Theater January 23, under the auspices of the Chicago Medical Society.

Dr Paul A O'Leary (Fellow), Rochester, Minn, has been elected Vice President of the newly formed American Academy of Dermatology and Syphilology. Dr Samuel Ayers, Jr (Fellow), Los Angeles, and Dr Everett S Lain (Fellow), Oklahoma City, were elected to its Board of Directors.

Among the speakers at the fifty-third annual session of the Mid-South Post Graduate Assembly, held at the Hotel Peabody, Memphis, February 15-18, Dr J H Means (Fellow and President), Boston, delivered a paper on "Treatment of Some of the Commoner Medical Emergencies" and Dr Russell L Haden (Fellow), Cleveland, delivered a paper on "Treatment of Anemia"

At the eighth annual conference of the American College of Radiology, held jointly with the Conference of Teachers of Clinical Radiology, at Chicago, February 13, Dr Byrl R Kirklin (Fellow), Associate Professor of Radiology, University of Minnesota (Mayo Foundation), and Secretary of the American Board of Radiology, delivered an address on "The Responsibility of the American Board of Radiology for Setting Up and Maintaining Standards in Radiologic Education" Dr Benjamin H Orndoff (Fellow), of Chicago, presented a paper on "The Bedside Manner in Radiology"

Under the Presidency of Dr Roscoe L Sensenich (Fellow), South Bend, Ind, the annual Northwest Regional Conference was held in Chicago February 13, the general subject of the Conference being "Medical Care for all the People" Dr Herman M Baker (Fellow), Evansville, Ind, addressed the Conference on "Preventive Medical Care as an Activity of County Medical Societies"

Dr Felix J Underwood (Fellow), Jackson, Miss, has been reappointed as executive officer of the Mississippi State Board of Health

Dr Walter Freeman (Fellow), Washington, D C, addressed the Missouri-Kansas Neuropsychiatric Association February 15 on "Experiments in Prefrontal Lobotomy in the Treatment of Mental Disorders"

Dr John Hamilton Crawford (Fellow), Assistant Professor of Pharmacology and Clinical Professor of Medicine, Long Island College of Medicine, Brooklyn, has been appointed Professor of Clinical Medicine and Director of the Long Island College division at Kings County Hospital

On February 9, 1938, Drs Anthony Bassler (Fellow) and Samuel Weiss (Fellow) of New York City, were decorated by the French Government with the Legion of Honor for their contribution to Medicine and Gastro-Enterology

Dr Joseph H Barach (Fellow), Pittsburgh, Pa, and Dr T E Newell, Dayton, Ohio, were the guest speakers at the annual banquet of the Stark County Medical Society at Canton, Ohio on Wednesday, February 9, 1938 The subject was "The Present Status of Medicine in the South American Countries"

Dr Clarence E de la Chapelle (Fellow), Assistant Professor of Medicine at the New York University College of Medicine, is serving as Acting Chairman of the Department of Medicine, pending the filling of the professorship, and as Acting Director of the Third Medical Division at Bellevue Hospital

OBITUARIES

DR SOLOMON LEON CHERRY

Solomon Leon Cherry (Fellow, 1920) died at his home in Clarksburg, W Va, October 21, 1937 of hypertensive heart disease, which first became manifest in January preceding

Dr Cherry was born in Russian Poland, April 10, 1887, and came to America with his parents in 1890. He attended Philadelphia and Baltimore Public Schools and graduated with the M D degree from the University of Maryland Medical School in 1908. He interned in Pathology at Bayview Hospital, Baltimore, 1908-09, and was resident in Pathology, Hebrew Hospital, Baltimore, 1909-10. He was Pathologist, Mt Sinai Hospital, Philadelphia, 1910-13. From 1913-18 he was Pathologist, St Mary's Hospital, Clarksburg, W Va. In 1918-19 he served overseas as a captain in the Army Medical Corps, where he was assigned to Evacuation Hospital No 24 as Chief of the Laboratory Service. After his discharge from the Army in 1919, he returned to Clarksburg as Pathologist, St Mary's Hospital, which position he held until the time of his death. He was Bacteriologist, City of Clarksburg Health Department, past President and Secretary, Harrison County Medical Society, a member of the West Virginia State Medical Association, of the Southern Medical Association, a Fellow of the American Medical Association, a Fellow of the American Society of Clinical Pathologists, a member of the Catholic Hospital Association, and Secretary of the Medical Advisory Board, St Mary's Hospital, Clarksburg.

Dr Cherry was always a student, earnest and hard-working, but rather retiring in disposition. Surviving are his widow and two sons.

WALTER E VEST, M D, F A C P,

Governor for West Virginia

DR GRAYSON EMERY TARKINGTON

Grayson Emery Tarkington, Fellow of the American College of Physicians since 1920, died at Albuquerque, New Mexico, Jan 12, 1938. Dr Tarkington was born at Oakland, La in 1894. He attended Hot Springs high school, Hot Springs, Ark, and graduated from the University of Maryland College of Physicians and Surgeons in 1917. During 1930 he pursued postgraduate work in psychiatry and neurology at the University of Colorado. He was formerly Chairman of the Medical Board, Director of the Out-Patient Department and Visiting Physician to the Leo N Levi Memorial Hospital, Hot Springs, formerly Chief of the Syphilis Staff of the U S Public Health Service Clinic, Hot Springs, also formerly a member of the House Staff of St Joseph's Infirmary, Hot Springs, formerly

President of the Garland County (Ark) Medical Society, formerly First Vice President of the Arkansas State Medical Society, Fellow of the American Medical Association, formerly Secretary of the Hot Springs Board of Health, formerly Associate Editor of the American Journal of Syphilis, member of Nu Sigma Nu Fraternity, served during the World War as First Lieutenant, Medical Reserve Corps, U S Army, author of many published articles. Because of ill health he removed to Albuquerque, N M, during 1933, where he became a member of the Staff of the Children's Home and Hospital, Southwestern Presbyterian Sanatorium and St Joseph's Sanatorium and Hospital.

Dr Tarkington was not merely a physician, he was a citizen. Many demands were made upon his crowded time by welfare, public health and similar activities, and he never failed to respond. As Director of the Out-Patient Department of the Leo N Levi Memorial Hospital he was as attentive to its details as to his private practice and much of the present success of this institution is due to his interest in its organization and functioning. His love of medical study induced him to serve as Associate Editor of the *American Journal of Syphilis* without compensation. In this capacity some two hundred medical journals were received monthly from which many of the articles were abstracted, filed and indexed. Few medical men had better command of current medical literature than he. When in 1933 he moved to Albuquerque, his generous and forceful personality was sadly missed in Hot Springs.

WILLIAM H DEADERICK, M D, F A C P,
Hot Springs, Ark

DR CHARLES EASTMOND

Dr Charles Eastmond (Fellow), of Brooklyn, N Y, died November 27, 1937, in the Peck Memorial Hospital, of carcinoma of the bladder.

Dr Eastmond was born in Brooklyn in 1879, and received his medical education at Columbia University College of Physicians and Surgeons, graduating in 1904. Early in his career he determined to follow the specialty of roentgenology, and proceeded to prepare himself along that line. For many years he was roentgenologist to the Carson C Peck Memorial and the Bushwick Hospitals, and consulting roentgenologist to the Kings County, Long Island College, Jewish, Jamaica and Nassau (Mineola) Hospitals and the Norwegian Lutheran Deaconesses' Home and Hospital. He contributed many papers dealing with roentgenology to medical journals, and was active in many medical societies. He was a member of the Medical Society of the County of Kings, the Medical Society of the State of New York, the Brooklyn Medical Association, the Brooklyn Pathological Society, the Medical Association of Greater New York, the Medical Club of Brooklyn, the Hospital Graduates Club of Brooklyn, Practitioner's Club of Brook-

lyn, the Associated Physicians of Long Island, the American Medical Association, the New York Roentgen Society, the American Roentgen-Ray Society, and had been a Fellow of the American College of Physicians since 1920

DR CHARLES D VER NOOY

Dr Charles D Ver Nooy, of Cortland, N Y, Associate of the College since March 10, 1923, died January 20, 1938, following a heart attack suffered the night preceding. He had been in poor health for the past year.

Dr Ver Nooy was born in Accord, Ulster County, New York, February 16, 1868, a descendant of early settlers there. His education was received in the public schools of Ulster County and the Cortland Normal School. For four years he taught school, after which he studied medicine at Syracuse University, graduating in 1892. He opened an office in Enfield, N Y, but later removed to Cortland in 1898. He early established a reputation for his diagnostic ability and keen observation in the medical field. In his early days his calls were made with horse and buggy. In 1912 he took over the old Cortland Hospital, remodeled it into the Ver Nooy Sanitarium and conducted it as a small hospital and as his private office.

Dr Ver Nooy was a member of the Cortland County Medical Society, the Medical Society of the State of New York and the American Medical Association. He became an Associate of the American College of Physicians in 1923. Outside of his medical work, he had been a pioneer in the extension of the telephone in his community, having been a Director and President of the old Cortland Telephone Company before its merger with the present system. Dr Ver Nooy had been a member of the local Board of Education since 1917, and for twenty years had acted as its President. He was a charter member of the City Board of Health, a Director of the Marine Midland Trust Company and Chief of the Staff at the Cortland County Hospital.

C F TENNEY, M D, F A C P,
Governor for Eastern New York

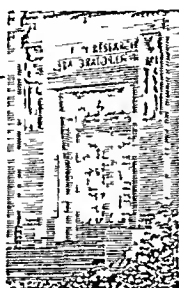
DR LORENA M BREED

Dr Lorena M Breed (Fellow), Pasadena, California, died October 20, 1937. She had been retired from medical practice for some time. Dr Breed was born at Washington, Iowa, in 1863, received her pre-medical training at the Central University of Iowa and graduated from the Northwestern University Woman's Medical School in 1893. She was early interested in clinical laboratory work. At one time she was connected with the Nalgonda Hospital in India, later returning to California. From 1895 to 1906 she again was in India, and connected with the Hyderabad State Deccan. From 1908 to 1914 she was in charge of the clinical laboratory

of the Pomona (Calif) Valley Hospital and from 1914, for several years, she was in charge of the clinical laboratory of the Pasadena (Calif) Hospital

Dr Breed was the author of several published articles and of a book entitled " The Human Machine, Its Uses and Abuses " She was a member of the Los Angeles County Medical Society, the California State Medical Society, the American Medical Association and the American Society of Bacteriologists She became a Fellow of the American College of Physicians on December 30, 1921

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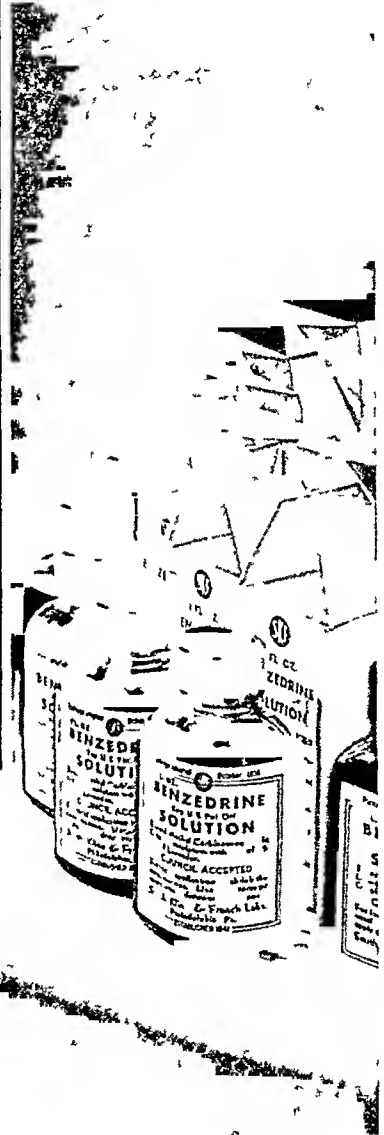
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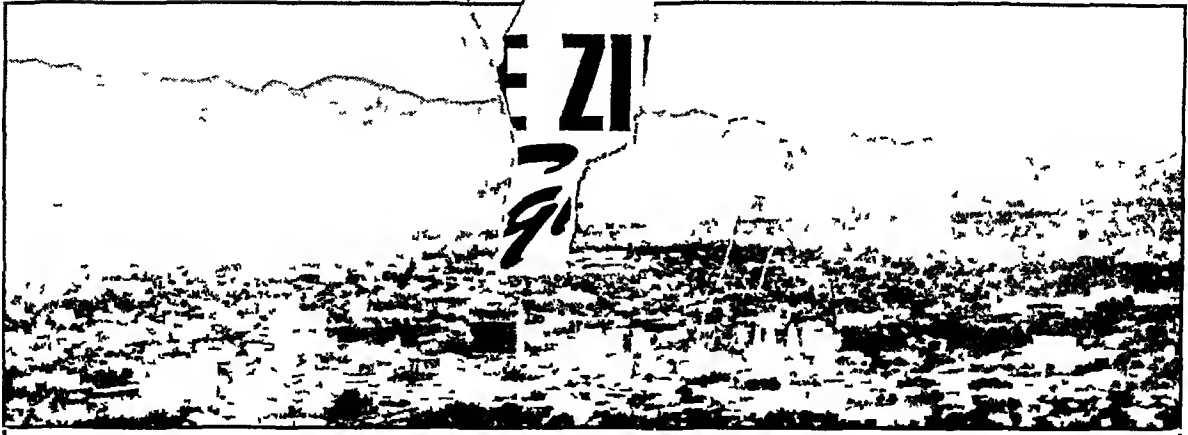
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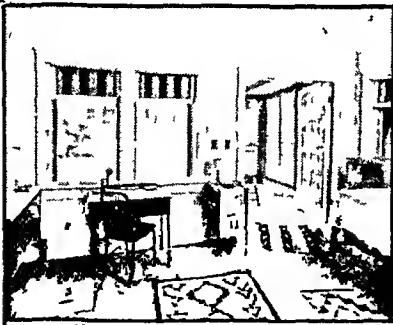
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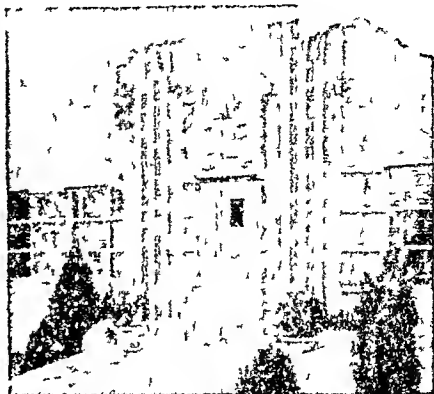
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Place of Publication—Prince and Lemon Sts, Lancaster, Pa

Editorial Office—University Hospital,
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Executive Office—4200 Pine Street,
Philadelphia, Pa

THE ANNALS OF INTERNAL MEDICINE is published by the American College of Physicians. The contents consist of contributions in the field of internal medicine, editorials, book reviews, and a section devoted to the affairs of the College.

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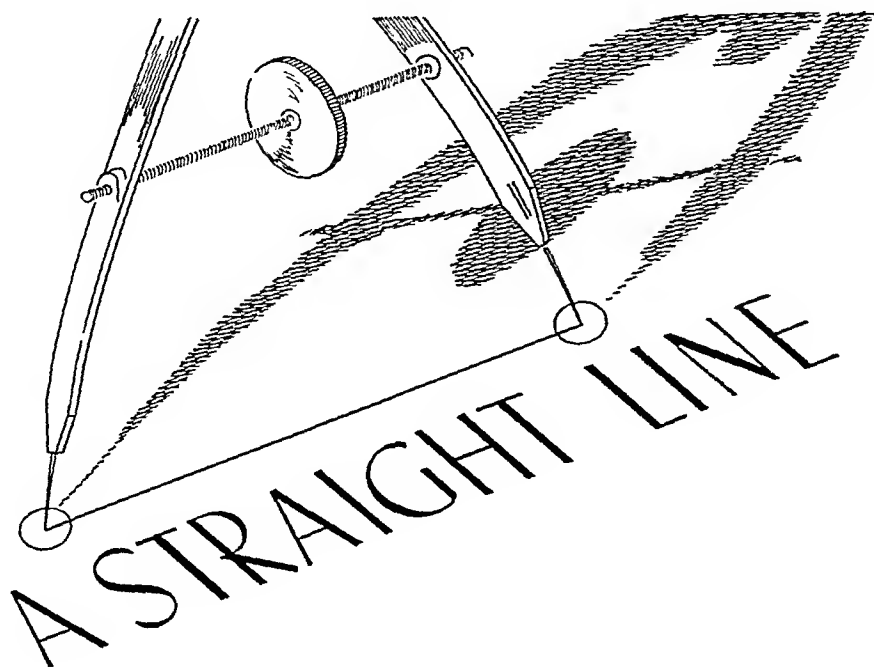
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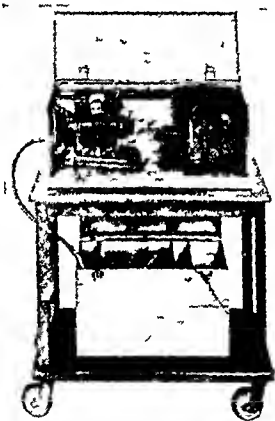
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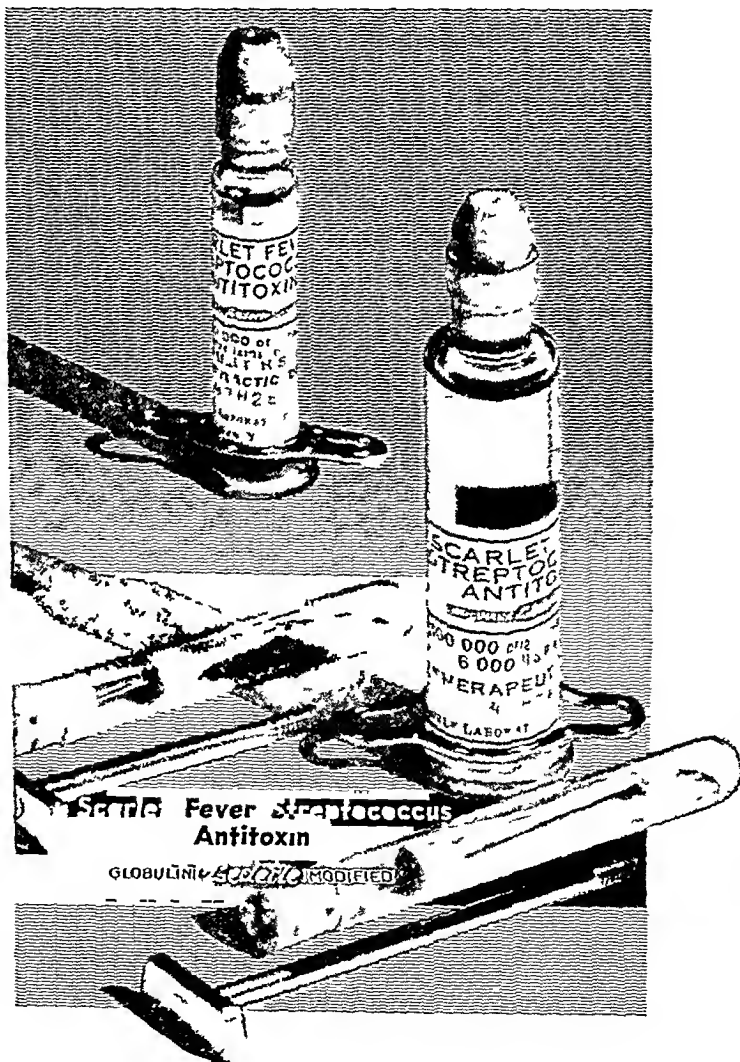
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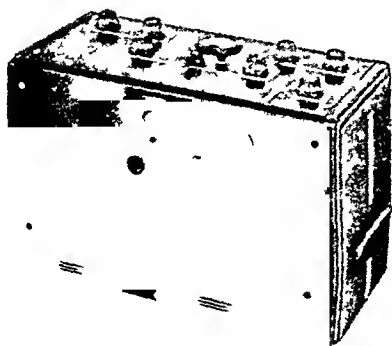
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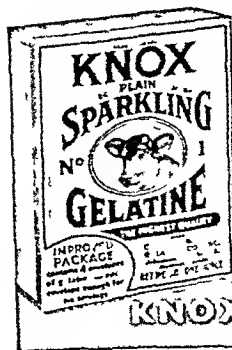
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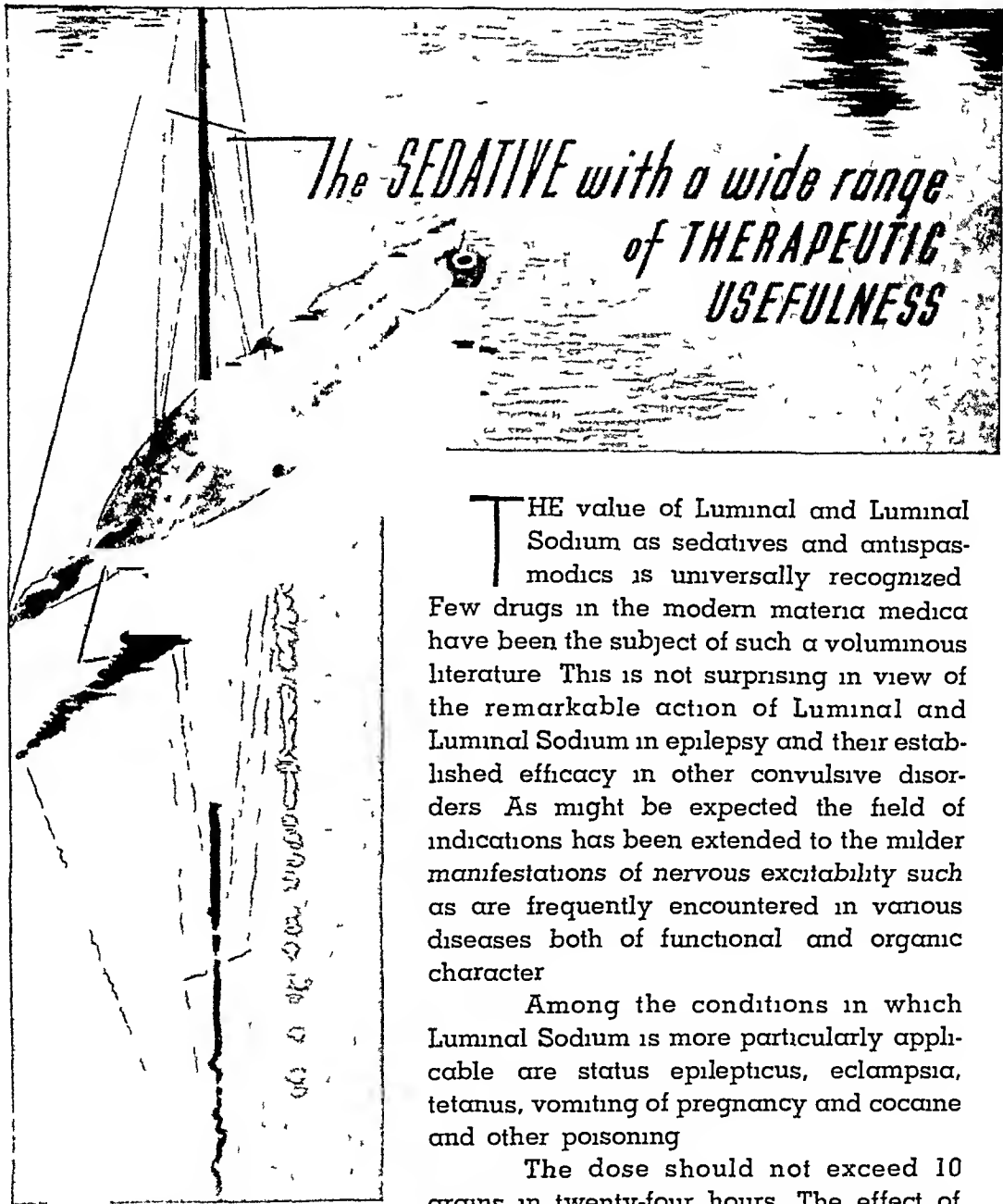
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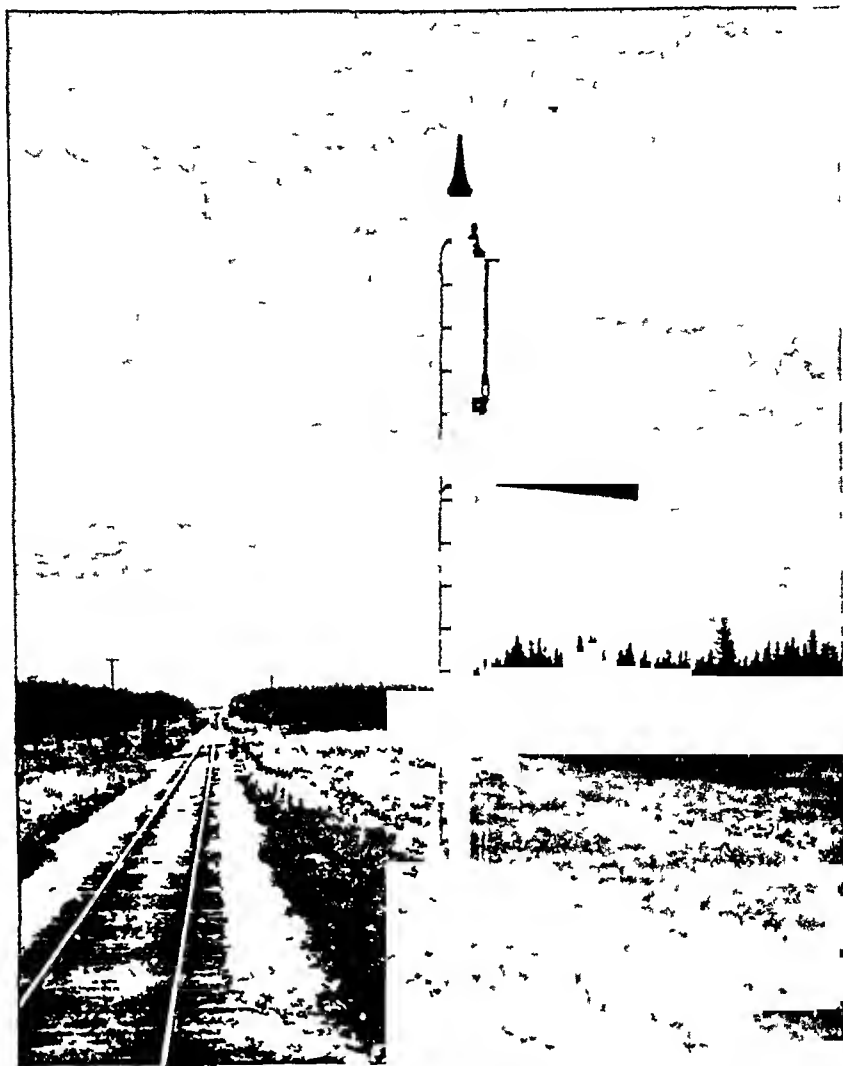
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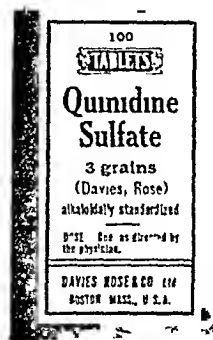
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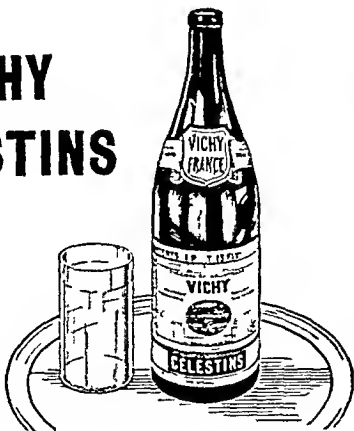
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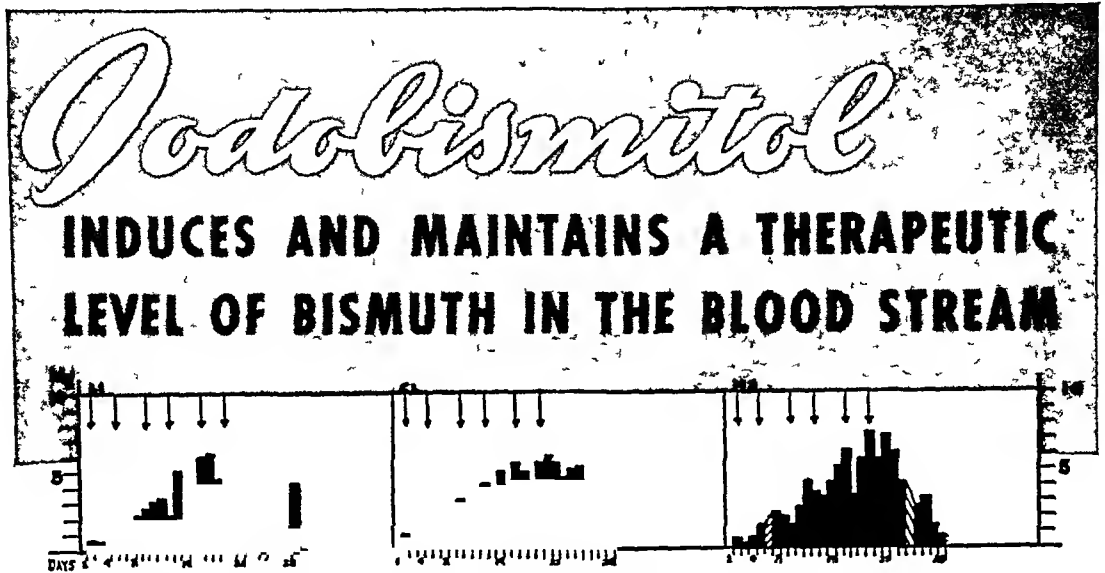
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¹ Sollmann T, Cole, H N, Henderson K, et al. *Amer J Syph Gon & Ven Dis* 21:480 (Sept), 1937.

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The high vitamin B content of Pablum assumes new importance in light of recent laboratory studies showing that avitaminosis B predisposes to certain gastro-intestinal disorders. Apropos of this, Cowgill says, "Gastric ulcer is another disorder which can conceivably be related to vitamin B deficiency. Insofar as the treatment of this condition usually involves a marked restriction of diet, the occurrence of at least a moderate shortage of this vitamin is by no means unlikely. Obviously the length of the period of dietary restriction is an important determining factor. Dalldorf and Kellogg (1931) observed in rats subsisting on carefully controlled diets that the incidence of gastric ulcer was greatly increased in vitamin B deficiency. Observations of this type merit serious consideration."²

Requiring no further cooking, Pablum is especially valuable during the healing stage of ulcer when the patient is back at work but still requires frequent meals. Pablum can be prepared quickly and conveniently at the office or shop simply by adding milk or cream and salt and sugar to taste. Pablum has the added advantage that it can be prepared in many varied ways—in muffins, mush, puddings, junket, etc. Further, Pablum is so thoroughly cooked that its cereal-starch has been shown to be more quickly digested than that of farina, oatmeal, cornmeal, or whole wheat cooked four hours in a double boiler (studies in vitro by Ross and Burrill).

In addition to all the above points Pablum has the advantage of being the only base-forming cereal (except Mead's Cereal which is the uncooked form of Pablum).

Pablum consists of wheatmeal, oatmeal, cornmeal, wheat embryo, alfalfa, yeast, beef bone, reduced iron and sodium chloride.

¹⁻² Bibliography on request

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ANNALS OF INTERNAL MEDICINE

VOLUME 11

APRIL, 1938

NUMBER 10

GRAVE SEQUELAE OF BLOOD TRANSFUSIONS, A CLINICAL STUDY OF 13 CASES OCCURRING IN 3500 BLOOD TRANSFUSIONS

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By the year 1910, the contributions to our knowledge of isohemagglutination made by Landsteiner, Shattock, Hektoen, Jansky, Moss, and others had laid the foundation for a great reduction in mortality from the transfusion of blood. The introduction of citrated blood by Agote, Weil, and Lewisohn during the World War, provided a much simpler method than had been in previous use. As a result of the reduction in hazards and the increase in technical facility, blood transfusion has become a common therapeutic procedure. The ease of administration and the relatively small mortality have unfortunately impressed many operators only with the innocuousness of the treatment. Despite the warnings of many writers, it must be true that serious complications have frequently occurred but have not received proper notice in the medical literature. A survey of recent publications on blood transfusion reactions indicates that interest in the subject is being reawakened.

The reactions following blood transfusion have been variously classified. Polayes and Lederer¹ have published an excellent review of the subject. Because of the lack of knowledge of the exact mechanisms involved, any etiological classification at present must necessarily contain potential errors. In this paper the various allergic manifestations, febrile reactions, and the transmission of disease will be ignored. The serious reactions which result in jeopardy of life or in permanent damage will be considered and illustrated with appropriate cases from our experience.

From November 1933 to July 1937, approximately 3,500 blood transfusions were performed in the University Hospitals of the State University of Iowa. Citrated blood was utilized almost exclusively. It was administered through small needles by gravity. All serious complications result-

* Received for publication October 15, 1937.

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ing from transfusion were studied as thoroughly as circumstances permitted. All transfusions were administered by the interns under supervision of the resident staff. No "transfusion teams" were utilized. The hospital maintained a donor list consisting mostly of the resident staff, interns, nurses, employes, and medical students. Beginning July 1, 1936, a physician in the bacteriology laboratory was made responsible for the determination of the blood groups of all donors and recipients except in the case of some emergencies. The interns performed the cross-matching of donors' and recipients' bloods under supervision. Most of the transfusions were given with bloods of the same group although bloods of Group O were occasionally used when the homologous group was not available.

RENAL INSUFFICIENCY FROM BLOOD TRANSFUSION

The syndrome of uremia with oliguria or anuria has long been known to occur, not only in hemolytic transfusion reactions but also in blackwater fever and in hemoglobinemia caused by various drugs such as quinine² and phenylhydrazine. The mechanism has been variously explained. Bordley³ discussed four theories which had been proposed. 1. Baker and Dodds⁴ suggested that the renal tubules become blocked by hemoglobin pigment precipitating in an acid solution. They produced the condition in rabbits and this work has been recently confirmed experimentally in dogs by DeGowin, Osterhagen, and Andeisch.⁵ The principal objection to this theory is that in many human cases not enough pathologic evidence of tubular obstruction can be found. 2. The renal lesions are the result of loss of chlorides similar to the cases described by Brown et al.⁶ Chemical study of many cases does not justify this explanation. 3. Longcope and Rackemann⁷ described cases with urticaria which developed renal insufficiency. It has been suggested that this mechanism might be involved in transfusion anuria. This is difficult to disprove save that the clinical syndrome can be reproduced in dogs with a single transfusion.⁵ 4. A nephrotoxic substance is released by hemolysis. This has no experimental proof at present. A fifth explanation has been introduced by the work of Mason and Mann⁸ and Hesse and Filatov⁹ which demonstrated a vasoconstrictor action of hemoglobin on the kidney. Hesse and Filatov believe that the renal damage is due to ischemia. The experimental work of the latter workers requires confirmation.

Most writers have agreed that the renal insufficiency following blood transfusion is dependent on hemolysis resulting from the administration of incompatible blood. Whether there is an alternative explanation in some cases remains to be proved. Cases of transfusion anuria have been reported where no incompatibility of bloods could be demonstrated by the usual laboratory methods and in which hemoglobinuria was not noted.^{10, 11, 12} Failure to demonstrate incompatibility in these cases can scarcely be ascribed to faulty technique as all of these tests were checked subsequent to the transfusion reactions, a situation which naturally constituted a stimulus to careful

work. A more plausible interpretation is that for a small number of bloods our present laboratory methods are inadequate to detect all incompatibilities. The absence of hemoglobinuria and jaundice does not constitute unequivocal evidence that hemolysis did not occur. Lichty, Havill, and Whipple¹³ have shown that there is a renal threshold for hemoglobin, and Drabkin, Widerman, and Landow¹⁴ have calculated that only about 10 per cent of the hemoglobin disappearing from the blood plasma is excreted in the urine. Two of our cases had hemoglobinemia two hours after transfusion reactions but in neither could hemoglobin be detected in the urine.

Undoubtedly the most common cause of the transfusion of incompatible blood is still the occurrence of gross errors in the preliminary cross-matching. It is difficult to conceive of any laboratory procedure in which an error can directly cause more disastrous results to the patient than in blood matching and blood grouping. Yet conversation with many interns graduated from various recognized medical schools reveals that they have only a very rudimentary and fragmentary knowledge of all procedures pertaining to the determination of blood incompatibility, transfusion technic, and transfusion reactions. In fact, a survey of the standard textbooks on laboratory diagnosis demonstrates that many of the presentations of the subject are inadequate reflections of our present knowledge. It has become necessary in this hospital to give lectures and laboratory demonstrations to each new class of interns.

CASE REPORTS

*Case 1*¹⁵ E. A., a 53 year old woman, had hemorrhages from the colon, probably as a result of roentgen irradiation for adenocarcinoma of the cervix uteri. Her blood was classified as Group O. In October 1931, she received transfusions from two Group O donors without reaction. In October and November 1933, three transfusions were given from different Group O donors with a febrile reaction following each. Preliminary cross-matchings by the hanging-drop method revealed no incompatibilities. The last transfusion was made with washed erythrocytes only. Immediately after transfusion she complained of severe pain in the neck, thighs, and abdomen. This was followed by a chill and the temperature rose to 103.2° F per rectum. Jaundice was evident within seven hours. The urine was diminished in volume and contained hemoglobin and granular pigment casts. The patient continued to vomit, she became drowsy and generalized edema developed. Death in coma occurred ten days after the transfusion. Permission for autopsy was refused. After the reaction had occurred the donor's and the recipient's bloods were re-typed and cross-matched. They were found to belong to Group O and no agglutination could be observed. There was some hemolysis of the donor's corpuscles by the recipient's serum, however. It is possible that more suitable laboratory methods might have demonstrated the incompatibility more satisfactorily.

Treatment. Intravenous injections of isotonic saline and hypertonic dextrose solutions, diathermy to the kidney regions, irrigation of the renal pelves with hot water, phlebotomy with withdrawal of 200 c.c. of blood.

Blood chemical studies shown in table on top of page 1780.

*Case 2*¹⁵ W. B., a 65 year old man, had bleeding from a duodenal ulcer. His blood was classified as Group O. During November 1933 he received two transfusions from donors who were supposed to belong to Group O. Preliminary cross-

Date 1933	van den Bergh	Blood Urea Nitrogen mg %	Blood Uric Acid mg %	Blood Crea- tinine mg %	CO ₂ Com- bining Power vol %	Plasma Chlor- ides mg %
November 1	4 4 indirect					
November 12		Transfusion				
November 13	17 4 direct					
November 14	0 9 direct	79 4	6 6	4 0	35 0	
November 15	0 9 direct	86 8	6 6	7 7	34 1	536
November 17		91 9	6 8	10 0		
November 19		94 5		12 0	26 8	555
November 20		100 0	10 0	11 5		
November 21		102 0	9 6	12 0	24 0	555
November 22			Died			

matching by the hanging-drop method revealed no incompatibilities. There was no reaction after the first transfusion. During the second transfusion, after 75 cc of blood had been given, the patient complained of a cramp in the thigh. A total of 500 cc of blood was given. One hour afterward he became nauseated and vomited, a slight chill was followed by a temperature of 100.4° F per rectum. Complete anuria developed. No jaundice was detected but examination of the blood plasma was not made until two days after transfusion. The patient continued to vomit, gradually become stuporous and died in coma 10 days after transfusion. Cross-matching of the recipient's blood with that of the last donor by the hanging-drop method revealed no incompatibility. Three years later, the donor's blood was typed with sera of high titer and found to belong to Group A. The donor stated that he had given eight transfusions as a Group O without reactions.

Treatment Isotonic saline intravenously and by hypodermoclysis, hypertonic dextrose intravenously, irrigation of the renal pelvis with hot water.

Autopsy The pathologist reported the significant lesions to be central necrosis of the liver lobules and necrosis of the tubular epithelium of the kidneys with some plugging of the lumina with debris and pigment.

Blood chemical studies

Date 1933	Blood Urea Nitrogen mg %	Blood Uric Acid mg %	Blood Crea- tinine mg %	CO ₂ Com- bining Power vol %	Plasma Chlorides mg %	van den Bergh
November 10	14 0	3 1	1 0	58 7	602	
November 25			Transfusion			
November 27	62 3	5 5	6 4	58 9	600	
November 28	80 5	6 5	8 3	56 0	595	0 2 indirect
November 29	88 9	8 5	10 7			
December 1	125 0	10 0	13 0	45 7	585	
December 2	141 4	10 0	15 5	35 2		
December 4	164 0	10 0	14 0	31 5		
December 5	193 4	10 0	17 6			
			Died			

Case 3 A Z, a 57 year old man, was admitted to the hospital November 28, 1934, in semi-coma. He had been known to have pernicious anemia for four years.

He was pale, disoriented, and afebrile. Extensive retinal hemorrhages were present. The blood pressure was systolic 125 and diastolic 75 mm of mercury. The urine contained some albumin, erythrocytes, and a few coarse casts composed of brownish pigment. Hemoglobin 38 per cent (Sahli), erythrocytes 1,650,000 and leukocytes 23,450 per cu mm, reticulocytes 17 per cent. The patient vomited frequently and developed edema of the ankles. The urinary volume for three days was 850 c c. He died in coma three days after admission.

Blood chemical studies

Date 1934	Blood Urea Nitrogen mg %	Blood Uric Acid mg %	Blood Crea- tinine mg %	CO ₂ Com- bining Power vol %	Plasma Chlorides mg %	van den Bergh
November 28	144.9	23.2	14.3			0.9 direct
November 30	155.4	18.5	12.3	25.8	587	0.8 direct

Treatment: Isotonic saline and hypertonic dextrose solutions intravenously.

Autopsy: The following anatomic diagnoses were made: hyperplasia of the bone marrow, hemosiderosis of the liver and spleen, slight chronic gastritis, degeneration of the posterior columns of the spinal cord, acute tubular nephritis (blood transfusion reaction), acute cholecystitis, acute myocarditis, passive congestion of the lungs, bilateral pleural effusion, old hemorrhages of cerebellum, polyp of sigmoid colon, emphysematous cystitis.

The pathologist was the first to suggest that the patient had died from a blood transfusion reaction. Subsequent correspondence with the referring physician revealed that on November 20 the patient had received 300 c c of whole blood from a type O donor. This was immediately followed by a severe chill and an oral temperature of 100.8° F. On November 23 he had received another transfusion of 250 c c of blood which was followed by a chill. Death, then, occurred 10 days after the first transfusion.

Case 4: A P, a 57 year old man, was admitted to the hospital December 31, 1934, with severe bilateral pyelonephritis, chronic cystitis, benign hyperplasia of the prostate, and bilateral ureteritis. An indwelling urethral catheter was placed and he was given ammonium nitrate, 14 grams (gr 22½) thrice daily, and serenum, five grains thrice daily. His blood was classified as Group O and was apparently compatible with that of the donor whose blood produced the fatal reaction in Case 2. On January 8, 250 c c of this donor's blood had been given to the recipient when the transfusion was discontinued because the patient developed a severe chill and oral temperature of 105.2° F. Anuria promptly developed. Vomiting and stupor intervened. On January 12 the condition was desperate. There was some edema of the lungs. In spite of that, it was thought that some risk should be taken in an effort to start urinary excretion. Thirty milligrams acetyl β methylcholine were given intravenously. The patient suddenly became much more dyspneic, apparently from increasing pulmonary edema. Atropine sulphate 0.13 mg (gr 1/50) was given intravenously with some relief of dyspnea for about two hours but then the extreme dyspnea recurred and the patient died (four days after transfusion).

The bloods of recipient and donor were again cross-matched by the hanging-drop method and no incompatibility was noted. As was reported in Case 2, the donor was proved three years later to belong to Group A when sera of high titer were used.

Treatment: Isotonic saline and hypertonic dextrose solutions intravenously,

roentgen irradiation of the kidney regions, acetyl β methylcholine Autopsy revealed advanced pyelonephritis

Blood chemical studies

Date 1935	Blood Urea Nitrogen mg %	Blood Creatinine mg %
January 2	43.4	5.8
January 5	48.3	6.0
January 8	53.9	5.4 Transfusion
January 9	74.2	8.1
January 10	83.3	9.3
January 11	101.5	11.0
January 12	105.7	11.4 Death

Case 5 E. S., a 50 year old woman, was admitted to the hospital with chronic glomerular nephritis. She was pale and slightly edematous. The retinæ were normal except for arteriosclerosis. The area of cardiac dullness was somewhat enlarged. Blood pressure systolic 170 and diastolic 100 mm of mercury. There was gross hematuria and moderate albuminuria. Hemoglobin 30 per cent (Sahli), erythrocytes 2,020,000, and leukocytes 8,400 per cu mm. The patient's blood was classified as Group A. On May 2, 1935, she was given 500 c.c. of citrated blood from a Group A donor without reaction. On May 6, another Group A donor gave her 500 c.c. citrated blood after preliminary cross-matching. During the administration of the last 50 c.c. she complained of some abdominal pain. Fifteen minutes later she had a chill and the rectal temperature was 104° F. The next day slight jaundice was noted. The urinary excretion became diminished and the hematuria continued until May 15 when the blood completely disappeared from the urine for the first time during hospitalization. There had been some vomiting since admission but on May 18 this became worse and she became comatose and dyspneic. Peripheral edema developed and the ophthalmologists noted papilledema and retinal hemorrhages. She died May 22, sixteen days after the transfusion.

The donor's and recipient's bloods were retyped and both were found to belong to Group A. However, the recipient's serum agglutinated and hemolyzed the donor's corpuscles as well as the corpuscles of an undoubted Group O. These reactions were evident both by the hanging-drop method and by the macroscopic method using small test tubes.

Treatment Hypertonic saline and dextrose intravenously, sodium bicarbonate intravenously, caffeine citrate intramuscularly, salyrgan intravenously.

Blood chemical studies shown in table on top of page 1783.

Autopsy Permission was granted only for examination of the kidneys. These showed a typical picture of an actively progressive diffuse nephritis with hemosiderosis of some of the tubular epithelium.

Case 6 A. E., a woman, 46 years old, entered the hospital with vaginal hemorrhage from a uterine fibroid. Hemoglobin 50 per cent (Sahli), erythrocytes 2,000,000 and leukocytes 11,000 per cu mm. Her blood was classified as Group A and, after preliminary cross-matching, she was given 500 c.c. of citrated blood from a Group A donor (Dr. H.) on July 7, 1936. A half hour later she had chills and the oral temperature rose to 104.2° F. There was considerable vomiting and an increase in amount of vaginal hemorrhage. On July 8 she received 550 c.c. citrated blood from her husband (Mr. E.) whose blood was typed as Group A and seemed compatible by cross-matching. The blood was given at 10 a.m. and was followed by some vomiting but no fever. In the late afternoon jaundice and oliguria were noted. The significance of the oliguria was difficult to evaluate because of the excessive out-

Date 1935	van den Bergh	Blood Urea Nitrogen mg %	Blood Uric Acid mg %	Blood Crea- tinine mg %	CO ₂ Com- bining Power vol %	Plasma Chlor- ides mg %
April 1		25.9		2.0		
April 5		30.8		2.9		
April 10		22.4	7.6	3.0		
April 15		26.6	7.2	2.5		
April 19		22.4	7.0	3.0		
May 2		21.0	5.1	2.5		
		Transfusion				
		Transfusion				
May 6		57.4	6.6	6.5	40.9	625
May 8	2.8 indirect	62.3	6.2	6.2		
May 9	3.2 biphasic	63.7	7.2	6.2		
May 10	2.1 biphasic	64.4	7.7	6.6		
May 11	2.4 biphasic	71.4		7.3		
May 12	2.2 direct	68.6	10.2	7.0		
May 13	2.3 direct	64.4	11.4	7.4		
May 14		62.3	10.0	7.7		
May 15	3.7 direct	65.0	11.4	8.1	39.0	625
May 16	3.0 direct	65.1	10.6	7.4		
May 17		64.4	10.4	7.7		
May 18		130.2	15.0	10.3		
May 22	3.5 direct				(Postmortem blood)	
		Died				

side temperature at the time. On July 11 the urinary excretion increased and, subjectively, the patient was better. She received another transfusion from a Group A donor July 12. This was followed by a chill and oral temperature of 103° F. There were no subsequent symptoms, however. On July 22, she received another transfusion from a sister (Group A) with no reaction. On July 27 a transfusion from another Group A donor (Dr. S.) was well tolerated. Vaginal myomectomy was performed July 27 and the patient made an uneventful recovery.

The bloods concerned in the reaction resulting in renal insufficiency were the patient's and those of the donors, Dr. H. and Mr. E. All of these bloods were retyped with sera of high titer and found to belong to Group A. The serum and corpuscles of each were cross-matched with all the others using the hanging-drop, the Vincent open slide method, and the Landsteiner centrifuge method. By none of these tests was any incompatibility ever shown. The possibility that distilled water instead of isotonic saline was added to the blood before transfusion was considered but could not be investigated directly. The stock solutions were tested and no errors in labelling were found.

Blood chemical studies shown in table on top of page 1784.

Treatment. Isotonic saline and hypertonic dextrose intravenously, blood transfusion, spinal anesthesia with procaine hydrochloride. Which of the first two transfusions produced the renal insufficiency is not known. The diuresis and fall in blood urea nitrogen were not prompt enough to be attributed to either transfusion or to the spinal anesthesia. It is the opinion of the clinicians in charge of the case that recovery was spontaneous.

Case 7. D. B., a 28 year old man, had a spastic torticollis following trauma to the head. His blood was classified as Group O. On June 17, 1936, an exploratory craniotomy was performed under avertin anesthesia. During the operation, shock developed and 450 cc citrated blood of Group O were administered in the operating room. Chills developed after he was returned to the ward. Another transfusion

Date 1936	Fluid In- take c c	Em- esis c c	Urine c c	Blood				
				van den Bergh	Urea Nitro- gen mg %	Uric Acid mg %	Creat- inine mg %	
July 7	1000	2050						Transfusion
July 8	3800	0	40	7 7 biphasic	53 9	6 8	3 4	Transfusion
July 9	2900	1375	619		67 9	7 0	5 0	Spinal anesthesia
July 10	3200	460	390	3 5 direct	73 5	8 0	5 0	
July 11	3400	225	1550		66 5		5 8	
July 12	2750	50	3400					Transfusion
July 13	4500	50	3635		62 3		5 0	
July 14	4800	0	2800	2 3 direct	56 7	5 6	3 2	
July 15	4500	0	1675		41 3	5 1	3 1	
July 16	3900	0	3425		24 5			
July 17	3500	0	2150					
July 20					9 8	2 8	1 2	
July 22								Transfusion
July 27								Transfusion

was given in the late afternoon and was followed by chills and rectal temperature of 105.8° F. The patient was unable to void. During the next three days he vomited and hiccoughed considerably. Another transfusion was given with Group O blood on June 19. The bloods seemed to be compatible on cross-matching. On June 20 he was still anuric and another transfusion was given. There was a sudden circulatory collapse which temporarily improved after the administration of epinephrine. The patient died three hours after the last transfusion (three days after operation). Just before death, a blood specimen showed the following: blood urea nitrogen 119.0 mg per cent, blood uric acid 8.0 mg per cent, blood creatinine 8.7 mg per cent, CO₂ combining power 23 vol per cent, plasma chlorides 600 mg per cent. Treatment. As the anuria was not recognized during life, no specific treatment was given. It seems probable, however, that the patient received some compatible blood after the reaction had occurred.

Autopsy. Anatomic diagnoses: Recent left partial cerebro-frontal lobectomy, intracranial hemorrhage, intraventricular hemorrhage, fatty metamorphosis of the liver with central degeneration, lobular pneumonia and edema of the lungs, acute gastric erosions, mild tubular nephritis (some hemoglobin pigment casts present).

The pathologist first made the diagnosis of transfusion anuria.

The treatment of renal insufficiency following blood transfusion reactions has been extensively discussed in the literature. The clinical course is such that the condition could be recognized in time to apply specific treatment were any known. Many procedures have been proposed and have been reported as successful in isolated cases: intravenous fluids both isotonic and hypertonic, diathermy and roentgen irradiation of the kidney regions, irrigation of the renal pelvis with hot water, phlebotomy¹⁶, intravenous sodium bicarbonate, spinal anesthesia¹⁷, decapsulation of the kidneys¹⁸, and transfusions of compatible blood¹⁹. It is notable, however, that some cases recover spontaneously while others die in spite of the therapeutic measures advocated.

Whether alkalinization of the urine prior to the transfusion will protect the kidneys from the excreted hemoglobin, if hemolysis occurs, is very difficult to prove statistically, because of the small incidence of such hemolytic reactions in any series. Baker and Dodds⁴ have shown that such a procedure protects rabbits, and DeGowin, Osterhagen, and Andersch⁵ have shown the same for dogs. It must be emphasized, however, that there are certain chemical differences between the blood of most animals and human blood which may complicate the application of this work to clinical practice. In the present state of our knowledge, however, alkalinization of the urine of the recipient before transfusion would seem a desirable precaution.

Tabulation of the treatment received in our seven cases developing renal insufficiency from transfusion reactions would seem to leave much to be desired in therapeutic efficacy. In none of these cases was decapsulation of the kidneys attempted.

Treatment of Transfusion Anuria

Treatment	Case Numbers						
	1	2	3	4	5	6	7
Isotonic saline intravenously	\	\	\	\	\	\	\
Hypertonic dextrose intravenously	\	\	\	\	\	\	\
Sodium bicarbonate intravenously					\		
Diathermy to the kidney regions	\						
Roentgen irradiation of the kidneys				\			
Irrigation of the renal pelvis	\	\					
Spinal anesthesia						\	
Phlebotomy	\						
Acetyl β methvlcholine				\			
Caffeine citrate intramuscularly					\		
Salyrgan intravenously					\		
Blood transfusion						\	\
Clinical data							
Maximum blood urea nitrogen mg %	102 0	183 4	155 4	105 7	71 4	73 5	119 0
Maximum blood creatinine mg %	12 0	17 6	12 3	11 4	11 4	5 8	8 7
Termination	Death	Death	Death	Death	Death	Recovery	Death

HEMOLYTIC REACTIONS WITHOUT RENAL INSUFFICIENCY

It is well recognized that all cases showing hemolysis from blood transfusions do not develop renal insufficiency. Under certain conditions which are not understood, the liberated hemoglobin is taken up by the tissues and a small amount is excreted through the kidneys without apparent harm.

CASE REPORTS

*Case 8*²⁰ E. H., a 25 year old woman, developed postpartum fever. Her blood was classified as Group AB. Because of the lack of donors of homologous group

she received blood from a donor of Group O. Preliminary cross-matching gave the expected result, i.e., the donor's serum agglutinated and hemolyzed the corpuscles of the recipient but the recipient's serum had no effect on the donor's cells. When 125 c.c. of citrated blood had been administered the patient complained of a feeling of constriction in the chest. The transfusion was promptly discontinued but extreme dyspnea and cyanosis ensued. There was a severe chill and the oral temperature rose to 106.2° F. Two hours later the patient's serum was tinged with hemoglobin and the van den Bergh reaction was 2.0 biphasic. No hemoglobin appeared in the urine and 36 hours later the van den Bergh was 0.5 indirect. The symptoms lasted only a few hours and the puerperal infection resolved by crisis. Examination of the donor's serum demonstrated an α hemolysin active in a titer of 1:12 to 1:20 and a corresponding agglutinin active in a dilution of 1:80. The β agglutinin was titered at 1:12.

Case 9 P. S., a 16 months old girl, with athrepsia and nutritional anemia was classified as blood Group AB, and received 150 c.c. of Group AB blood after preliminary cross-matching had shown no incompatibility. Three and one-half hours later the rectal temperature rose to 104.5° F and the pulse was 140 per minute. Hemoglobin was found in the urine. The bloods were retyped and again both classified as Group AB. The recipient's serum, however, was found to agglutinate the donor's corpuscles. The same serum was tested against the corpuscles of several bloods of Groups A and B. It agglutinated most Group B cells but not those of Group A. Two weeks later another transfusion of 150 c.c. of another Group AB blood was given. The rectal temperature rose to 102° F but no hemoglobinuria was noted. The patient made an uneventful recovery.

Case 10 K. A., a 26 year old woman, had pyelitis of pregnancy with intermittent fever. Her blood was classified as Group B. On May 28, 1936 she received 500 c.c. of citrated blood from a Group B donor. This was followed by a chill and an oral temperature of 104° F. On June 16 500 c.c. of blood from another B donor were given. The urine had been alkalinized prior to transfusion. Fifteen minutes later she had a chill with nausea and vomiting. The oral temperature rose to 102.4° F. The next morning she appeared deeply jaundiced. By three in the afternoon the icterus had noticeably diminished. No hemoglobin was found in the urine. Early on June 18 spontaneous labor occurred and a premature infant was delivered which soon died. The patient made an uneventful recovery. Repetition of the cross-matching showed no incompatibility.

Blood chemical studies

Date 1936	van den Bergh	Blood Urea Nitrogen mg %	Blood Uric Acid mg %	Blood Creatinine mg %
June 16	0.3 direct	Transfusion		
June 17	20.1 direct		33.6	1.6
June 18	8.2 direct		25.9	1.4
June 21	1.0 biphasic		28.0	2.0
June 26			29.4	1.2

PULMONARY EDEMA FOLLOWING BLOOD TRANSFUSION

In addition to the pulmonary edema which constitutes one of the terminal features of uremia from any cause, it has been commonly recognized that overburdening of the circulation with large volumes of fluid sometimes pro-

duces the condition directly²¹ Plummer²² recently reported five deaths from pulmonary edema after blood transfusions in Charing Cross Hospital

Case 11 E S, a woman 30 years old, entered the hospital with a septicemia due to *Streptococcus hemolyticus*. She was suffering intense pain from a thrombophlebitis in a large cavernous hemangioma involving the entire right arm. The heart was normal in size and rhythm by the usual physical diagnostic criteria. There was a soft, blowing, systolic murmur at the cardiac apex. The lungs were clear. A moderate secondary anemia was present. Her blood was classified as Group A. After preliminary cross-matching on February 21, 1937, she received 500 c c of citrated blood from a Group A donor along with 200 c c of isotonic saline solution. The administration of the solutions required one hour and 10 minutes. There were no immediate symptoms but about one hour later she became extremely dyspneic and cyanotic and complained of indefinite pains in the thighs and legs. The heart appeared normal except for a rate of 130 per minute. Some coarse râles were present in the left lung. The symptoms were partially alleviated for a time by the administration of 0.5 c c epinephrine hydrochloride, 16 mg (gr $\frac{1}{4}$) morphine sulphate, and atropine sulphate 0.4 mg (gr $\frac{1}{50}$) but she died eight hours after the transfusion was begun.

The donor's and recipient's bloods were re-typed and re-cross-matched after the transfusion using the hanging-drop, Vincent open slide, and the Landsteiner centrifuge methods. No incompatibility could be demonstrated.

Autopsy The anatomic diagnoses were *Streptococcus hemolyticus* septicemia, cavernous hemangioma of right shoulder and arm, pulmonary edema and congestion. There was no cardiac dilation.

Case 12 H H, a woman, aged 43 years, had chronic glomerular nephritis with secondary anemia. Before admission she was said to have had hypertension but during her stay in the hospital the blood pressure was about 140 mm of mercury systolic and 70 mm diastolic. The heart was moderately enlarged and there was slight pitting edema of the ankles. The urine contained a moderate amount of albumin and a few leukocytes. No casts were seen. The hemoglobin measured 27 grams (Haden-Hauser), erythrocytes numbered 1,300,000 and leukocytes 21,200 per cu mm. Her blood was classified as Group A. February 22, 1937, she was given a transfusion of a mixture of 450 c c of Group A citrated blood and 150 c c of isotonic saline. When 200 c c of the mixture had been given in 45 minutes, the administration was discontinued because of severe dyspnea and cyanosis. She was given epinephrine hydrochloride and morphine sulphate hypodermically and aminophyllin (0.48 gram) intravenously. She died one-half hour after the transfusion was discontinued. Analysis of postmortem blood gave the following values: urea nitrogen 99.4 mg per cent and creatinine 11.8 mg per cent.

The recipient's and donor's bloods were re-typed and re-cross-matched after the reaction occurred but no incompatibility could be demonstrated by the hanging-drop, Vincent open-slide, or the Landsteiner centrifuge methods.

Autopsy Anatomic diagnoses—marked pulmonary congestion and edema, slight cardiac hypertrophy, chronic diffuse nephritis, anemia and hyperplasia of the bone marrow. The heart was only moderately dilated. It is very difficult to account for the production of pulmonary edema by increasing the blood volume by only 200 c c.

RETINAL HEMORRHAGE FOLLOWING TRANSFUSION

Ophthalmologists are acquainted with the fact that blood transfusions are occasionally followed by retinal hemorrhages²³. The only statistical study available is that of Messinger and Eckstein²⁴ who examined the retinae of 60 individuals preceding and following transfusion with com-

patible blood. Ten of these patients developed retinal hemorrhages after transfusion. There was a high incidence of blood dyscrasias in the series studied, however, and the hemorrhages were most common in this group. Walker,²⁵ of the Department of Ophthalmology of this hospital, is at present engaged in a similar study of cases receiving transfusions. The incidence of blood dyscrasias in his series is very much lower and, so far, out of over 80 cases examined only one has developed retinal hemorrhages. The cases to be reported here are not included in his series.

CASE REPORTS

Case 5 This has been reported above. She developed retinal hemorrhages after transfusion and during the time that there was evidence of renal insufficiency from the chronic nephritis as well as from the superimposed transfusion oliguria.

Case 3 This man had pernicious anemia and received the incompatible blood before admission to the hospital. He had extensive retinal hemorrhages but whether they followed transfusion is not known.

Case 13 A W, a woman of 69 years, had an anemia of unknown etiology. The hemoglobin was 30 per cent (Sahli), erythrocytes numbered 1,060,000 and leukocytes 4,800 per cu mm. The leukocytes were predominately lymphocytes with an occasional myelocyte and blast cell. The blood Kahn and Wassermann tests were negative. Achlorhydria was demonstrated after histamine stimulation. The tourniquet test for petechiae, the bleeding and coagulation time, and erythrocyte fragility tests were all normal. The clot was non-retractile. The blood platelets were 0.09 per cent (Van Allen), and the hematocrit 12 per cent. Liver therapy did not stimulate reticulocytosis. There was a continuous low-grade fever. The tentative diagnosis was aleukemic leukemia, lymphatic type. Before transfusion fairly extensive hemorrhages were seen in both retinæ but the maculae were not involved. The patient's blood was classified as Group A and on November 27, 1935, she received 500 c.c. of citrated Group A blood in 45 minutes, after preliminary cross-matching. Thirty minutes after transfusion there was a violent chill and the rectal temperature rose to 105° F. The next morning she complained of inability to see objects at a distance of 18 inches. Ophthalmoscopic examination revealed great extension of the pre-retinal hemorrhages to include both maculae. There was no hemoglobinuria or icterus and re-cross-matching of bloods by microscopic and macroscopic methods revealed no incompatibility.

She received 500 c.c. of blood from another Group A donor on December 3, with no reaction. On December 10 the bleeding time had become greatly prolonged and petechiae were elicited by the tourniquet test. On December 13 a transfusion of 400 c.c. of blood from another Group A donor had to be discontinued because of a chill and rectal temperature of 104.5° F. She died December 16, apparently of bronchopneumonia. No autopsy could be obtained. No incompatibility of bloods could be demonstrated in the laboratory after any of the transfusions.

SUMMARY

Mortality Seven deaths directly attributable to blood transfusions occurred in a series of approximately 3,500 transfusions. Five persons died of renal insufficiency and two of pulmonary edema (Case 3 should not be included in the statistics because the transfusion was given in another hospital). The mortality for blood transfusion in this series was, therefore, 0.2 per cent. Only one individual developing renal insufficiency in

this series recovered (Case 6) and this could not clearly be attributed to any treatment received

Transfusion of Incompatible Blood Many authors¹ have emphasized the importance of using typing sera of high titer. This is further illustrated by the donor in Cases 2 and 4 who gave blood as a Group O and later, with stronger sera, was found to belong to Group A. We have had five or six individuals on the donor list who were originally thought to belong to Group O but when retyped with stronger sera were found to belong to other groups, mostly to Group A.

The necessity for the cross-matching of bloods in addition to the typing is well recognized. This is further illustrated in Cases 5 and 9 where the recipients were found to belong to atypical blood groups which were not differentiated by strong typing sera and in which errors apparently occurred in the preliminary cross-matching.

Interviews with interns graduated from various medical schools and a review of their performance in managing large numbers of transfusions lead to the following conclusion. Either the importance of the laboratory technic of determining blood incompatibility is under-emphasized in undergraduate medical education or the technic itself is too difficult to be entrusted to those with the laboratory training of the average intern. Neither of these views is implied in the discussions contained in the standard textbooks on laboratory diagnosis.

It seems necessary further to emphasize the dictum that a transfusion should be discontinued immediately upon the occurrence of any unusual symptoms. This is illustrated by Cases 2 and 5 in which symptoms were ignored or considered insignificant and in Case 8 in which the transfusion was discontinued in time to prevent serious results.

Hemolytic Transfusion Reactions We have collected considerable data regarding the van den Bergh reaction in cases of hemolysis (Cases 1, 5, 6, 8, 10). These would indicate that for the first day or so after hemolysis occurs the van den Bergh is either "direct" or "biphasic" and may attain values as high as 20.1. It promptly thereafter changes to an "indirect" reaction within the limits of normal. This conclusion coincides with the statement of Mann and Bollman.²⁶

Cases 8 and 10 and the experimental demonstration of a renal threshold for hemoglobin justify the conclusion that the most reliable diagnostic criterion of a hemolytic transfusion reaction is the occurrence of hemoglobin-tinged blood serum one or two hours after the transfusion rather than the appearance of icterus or hemoglobinuria.

Both from our experience and that of other writers, we must conclude that the present laboratory tests as routinely applied involving cross-matching by the hanging-drop, the Vincent open-slide, and the Landsteiner centrifuge methods are inadequate in certain instances to detect incompatibilities of bloods which after transfusion become manifest clinically. This is especially illustrated by Case 6.

Renal Insufficiency from Blood Transfusion The various theories to account for the mechanism of this phenomenon are discussed. If it is admitted that hemolytic reactions can occur without hemoglobinuria, the dogma that anuria occurs only after hemolysis cannot be proved or disproved by our studies or by the cases reported elsewhere in the literature. In all of our cases of renal insufficiency in which the blood serum was examined promptly, the van den Bergh reaction was compatible with the diagnosis of hemolysis.

In view of our ignorance of the mechanism of the renal damage it would seem that the only safe procedure at present is to alkalinize the urine prior to transfusion. This has been shown to prevent obstruction of the renal tubules by hemoglobin in rabbits and dogs. It must be assumed for the present that this mechanism also operates, at least occasionally, in humans.

The treatment of this type of renal insufficiency is at present unsatisfactory. Some cases recover spontaneously and others probably die regardless of any known therapeutic procedures. We have not attempted decapsulation of the kidneys but it has been reported to have failed in some cases. Apparently more efficient treatment depends on increasing our knowledge of the pathogenesis.

The Use of "Universal Donors" This procedure is fraught with danger unless the agglutinins of the donor have been previously titrated and found to be weak (Case 8).

Pulmonary Edema from Blood Transfusion This complication of blood transfusion has been neglected in the medical literature. It is not the result of the administration of incompatible blood. On theoretical grounds, it would seem to be due to overburdening of the right side of the heart although it is difficult to ascribe this explanation in Case 12 where only 200 c c of fluid apparently produced death. It is possible that an amount of pulmonary edema small enough to escape detection was previously present. At autopsy the heart in Case 12 was only moderately dilated and in Case 11 no dilation could be found. Patients with cardiac damage and those with nitrogen retention from any cause apparently tolerate transfusions poorly.

Retinal Hemorrhages after Blood Transfusion In patients having diseases which predispose to retinal hemorrhage, as in blood dyscrasias, transfusion is sometimes followed by bleeding into the macular region causing serious impairment of vision (Cases 3, 5, and 13).

Diagnosis of Transfusion Reactions by the Pathologist The importance of careful postmortem examination has been stressed. Autopsies of patients receiving transfusions are occasionally very illuminating if the pathologist is familiar with the morbid anatomy of transfusion reactions. This is especially true in cases of renal insufficiency. Cases 3 and 7 were first diagnosed by the pathologist when the condition had not been suspected clinically.

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CHRONIC ATROPHIC ARTHRITIS *

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THERE has been sufficient interest and study of arthritis to warrant a somewhat detailed report on chronic atrophic arthritis. This terminology is synonymous with Type I, chronic infectious, chronic proliferative, chronic rheumatoid arthritis and arthritis deformans.

This study includes an admission analysis of 343 patients and a treatment and follow-up summary of 274 patients seen at this clinic. It does not include 280 patients a recent study of whom has been reported ^{1, 2}

The patients in this study include only those having a definite chronic atrophic arthritis of the non-specific type. All other types were carefully excluded. The availability of data elsewhere ^{3, 4, 5, 6, 7, 8, 9} justifies the omission in this paper of discussion of the diagnostic criteria of atrophic arthritis.

A thorough history, physical and laboratory examinations were done on these patients on admission and at monthly intervals thereafter. The laboratory data required were complete blood counts, sedimentation rates (Westergren), agglutination titers of serum (reaction with standard strains of streptococci of the hemolytic and viridans type), complete stool and urine examinations and cultures and smears from foci of infection. In addition, roentgenological examination (fluoroscopic and films), metabolism tests, and blood chemistry determinations were done when indicated.

The findings on admission are summarized in table 1. They will be discussed under their separate headings.

TABLE I
General Summary

	Males	Females	Both sexes
Total patients seen	153 (44.6%)	190 (55.4%)	343
Total patients admitted			274 (76.96%)
Total patients diagnosis only			69 (23.04%)
Average age when seen	42.7 years	44.2 years	43.56 years
Oldest patient	89 years	78 years	89 years
Youngest patient	18 years	6 years	6 years
Average age at onset	36.59 years	37.28 years	36.93 years
Average duration of arthritis when seen	6.11 years	6.92 years	6.51 years
Patients showing deformities	91 (44.66%)	115 (55.34%)	206 (60.06%)
Patients showing no deformities	62 (45.25%)	75 (54.75%)	137 (39.94%)
Patients having focal infection			198 (57.73%)
Patients with no demonstrable focal infection			145 (42.27%)

* Received for publication April 26, 1937
From The Wyatt Clinic and Research Laboratories, Tucson, Arizona
Presented in part before the Chicago Orthopaedic Society, April 1937

INCIDENCE BY SEX

Out of 343 patients 44.6 per cent (153) were males and 55.4 per cent (190) were females. These percentages do not show as great a preponderance in the female as compared to the males as the figures quoted by some investigators¹⁰, however, they are closely comparable to the percentage incidence reported by Weatherby¹⁰. All agree that atrophic arthritis is higher in the female¹¹.

AGE OF PATIENTS AT THE ONSET OF ARTHRITIS AND AGE ON ADMISSION

The average age of male patients at the onset of the disease was 36.59 years, for females the average age at onset was 37.28 years, with an average age of 36.93 years for both sexes. The latter figure represents a mean between two extremes of age, namely, two years and 71 years. The highest incidence for both sexes was between the third and fourth decades of life. No important difference in sex in this regard was noted.

The average age of patients when first seen at this clinic was for males 42.7 years and for females 44.2 years with an average age of 43.56 for both sexes. The oldest patient seen was a male of 89 years, the youngest patient seen was a female aged 6 years.

The above summary indicates that although the highest incidence is between the third and fourth decades of life the disease may occur at any age and in either sex. Furthermore, no one age group is exempt.

DURATION OF ARTHRITIS PRESENCE OF DEFORMITIES

The chronicity of atrophic arthritis is quite evident when one notes the duration of the disease in this group of patients. The average durations of the arthritis when these patients were first seen were for males 6.11 years and for females 6.92 years, with an average duration of 6.51 years for both sexes.

Deformities were present in 60.06 per cent of these patients. The females exhibited a slightly higher incidence (55.34 per cent) than the males (44.66 per cent).

From this it is apparent that this disease is more or less progressive and that deformities are prone to occur. A study of the case histories of these patients indicates that the majority were "last resorters"—patients who had been under the care of competent men elsewhere—patients who had been to various spas and health centers—patients who had tried various patent medicines or other remedies obtainable—patients who came here with the final fond hope that the climate in some miraculous manner would alleviate their suffering, restore damaged joints to function or even "cure" their arthritis. It has been our unhappy experience to see patients who were sent or came here for climatic benefit during the active stage of the disease who did not think it necessary or were not advised that competent medical

supervision should be continued as long as the arthritis is active. It is amazing how fast these people without adequate treatment develop deformities. It finally becomes apparent to the patient that he is getting worse and he presents himself for medical care. How much easier it is to prevent than correct a deformity, but successful prevention is absolutely dependent upon early continuous treatment.

We must ever be on the alert—to have sufficient foresight to know that without adequate management flexion contractures, ankylosis and deformities will probably occur. In addition, it is highly important that these patients remain a sufficient time at one place, otherwise they will develop their deformities during their pilgrimage from doctor to doctor.

FOCAL INFECTION

An extensive and thorough search for foci of infection was made in this study. Out of this group 57.73 per cent (198 patients) were found to have definite demonstrable focal infection. This is a surprisingly high incidence in view of the chronicity of these cases and the low incidence reported by other workers.¹²

In table 2 are indicated the sites of the focal infections.

TABLE II
Location of Foci of Infection

Total cases 343	Cases with foci 198				57.73 per cent
Throat or pharynx	alone	19.0%	with other foci		23.0%
Sinuses	alone	9.0%	with other foci		19.0%
Gingival tissue	alone	5.5%	with other foci		13.0%
Tonsils or remnants	alone	8.0%	with other foci		10.0%
Teeth	alone	6.5%	with other foci		10.0%
Urinary tract	alone	8.0%	with other foci		10.0%
(Lower) Respiratory tract	alone	5.5%	with other foci		5.7%
Female pelvis	alone	4.0%	with other foci		4.5%
Prostate	alone	4.0%	with other foci		4.0%
Gall-bladder	alone	1.5%	with other foci		1.5%
Colon	alone	0.0%	with other foci		1.0%
Miscellaneous	alone	0.0%	with other foci		0.0%

In 80 per cent of the cases the foci were found alone or in combination from the respiratory tract up. Of this 80 per cent localizations in the throat or pharynx were most commonly observed. Sinuses, gingival tissue, teeth and respiratory tract followed in the order of their respective incidence. In the remaining 20 per cent the urinary tract was involved in one half of the cases, followed by female pelvis, prostate, gall-bladder and colon in the order presented.

The highest incidence in this series is that of the throat and pharynx. The relatively low incidence of infection in tonsils as compared to that found

by other workers⁹ is due to the fact that most of these patients had had their tonsils removed

Inflammation of the throat is often so slight as to escape the notice of the physician and patient. Rarely does the patient complain of a sore throat. We have cultured all these throats. In a large number of instances the flora have contained a predominating or even pure culture of hemolytic streptococci. In search for other foci one must look to tonsils or tonsillar remnants, the sinuses, the gingival tissue and teeth. The examination of the teeth and gingival tissue should include not only roentgenological study but also careful direct examination and transillumination. The gingival tissue should be massaged and carefully inspected for pus pockets and faulty dental repair. Cultures should be done on all suspicious areas. Once a focus of infection has been found it is always necessary to determine by further search if it is primary or secondary.

It has been repeatedly brought to our attention in this study that (1) periodontoclasia may be the only focus present, that (2) the incidence of gingival infection is higher than that of dental abscess, and that (3) roentgenological examination of the teeth will but in a few cases definitely demonstrate periodontal infection.

Although sinusitis has been looked upon as a fairly benign factor in atrophic arthritis, the high incidence reported here may indicate otherwise. Its importance has been indicated by the studies of others^{13, 14}.

In most of these foci we were able to demonstrate streptococci, usually of the hemolytic type, except in the infections of the urinary tract. Cholecystographic and non-surgical gall-bladder drainage evidence of gall-bladder infection was confirmed by direct examination and culture of tissue removed at operation.

The actual significance of these findings is not clear—there has been no direct evidence of their relationship to atrophic arthritis, particularly in long existing cases, yet we are firmly convinced that focal infection is important even in chronic cases. If one considers atrophic arthritis as due to three general factors, namely, infectious, external and constitutional, he may hope to remove the first and indirectly benefit the third. We have in several instances removed foci of infection in long standing cases with remarkable results. It has happened too frequently to be coincidental, however, we are at a loss to know whether the effect was due to removal of the infectious factor or to the constitutional improvement. Until we have direct evidence of the relationship of bacteria to this disease little can be stated with assurance, although it may be discussed at length.

TREATMENT

This group of patients has received a composite treatment as indicated in table 3. We wish to emphasize that no single treatment is specific in this group.

TABLE III
Treatment Summary

Patients treated		274
Receiving	Physiotherapy	}
Receiving	Dietotherapy	
Receiving	Heliotherapy	
	or	
Receiving	Combination of above	69
	or	
Receiving	None of above	4
Receiving	Antigen, intravenously	122
Receiving	Vaccine	40
	or	
Receiving	Both	15
	Removal or treatment	
Receiving	Focal infection	198
	Non-operative orthopedic	
Receiving	Treatment	118
	Operative orthopedic	
Receiving	Treatment	11
Receiving	Blood transfusions	48

An ideal treatment plan embraces a composite program directed to the relief of pain, the amelioration of clinical manifestations, the arrest, the prevention and the correction of deformities. In table 4 an outline of treatment is given. Over a period of several years in which such a procedure has been followed we have found it most valuable.

The treatment of atrophic arthritis involves not only the active treatment but also the prophylactic treatment. We have little information in regard to the prevention of this disease, but we are convinced that the incidence of chronic cases is much too high. Unfortunately we have no means at our disposal to say which patient under certain circumstances will develop arthritis and which one will not.

Constitutional treatment is an important phase of active therapy. It involves treatment or removal of focal infections, rest, physical therapy, dietotherapy, blood transfusions, heliotherapy and climatotherapy.

Of great interest is the fact that an intercurrent jaundice may produce a remission in arthritis. For the past year and a half we have been working on the problem of "therapeutic jaundice." Recently we have evolved a technic whereby a "therapeutic jaundice" may be induced safely and with very slight reaction, either local or general. The importance of jaundice in arthritis has already been discussed by various authors in the literature. We will shortly present a paper on this subject.

REMOVAL OR TREATMENT OF FOCAL INFECTIONS

In all patients in this group in whom a definite focal infection was demonstrated this focus was treated or, when feasible, removed. Out of this group 82 per cent exhibited moderate to marked improvement on discharge, while 18 per cent of this group exhibited slight to no improvement.

TABLE IV
Treatment of Atrophic Arthritis

An ideal treatment plan embraces a composite program directed to the amelioration of the manifestations of a symptomatic and constitutional disease

I Prophylactic

A Removal or correction of

- 1 Infectious factors—early treatment or removal of focal infections before symptoms appear
- 2 External factors—avoidance of chilling, damp climates, trauma etc
- 3 Constitutional factors—proper attention to constitutional inadequacy—conversion of the “arthritic soil” into a “non-arthritic soil” by detailed attention and treatment

II Active

A Constitutional

- 1 Treatment or removal of focal infections
- 2 Rest
- 3 Physical therapy
- 4 Diet
- 5 Transfusions
- 6 Heliotherapy
- 7 Climatotherapy

B Local—Prevention of Deformities

- 1 Rest to inflamed joints, either bed rest or by proper orthopedic appliances or both
- 2 Motion—early through painless range to prevent ankylosis, later active exercise to restore muscle tone

C Correction of Existing Deformities

1 Non-operative

- a Traction
- b Cast wedging
- c Turnbuckle and other adjustable splints
- d Manipulation
 - 1 With anesthesia
 - 2 Without anesthesia

2 Operative

- a Arthroplasty
- b Capsuloplasty
- c Tendon lengthening or shortening
- d Osteotomy
- e Synovectomy
- f Arthrodesis, etc

D Antigens and Vaccines

E Drugs

1 Non-toxic

- a Salicylates
- b Iron
- c Rarely opiates (caution)

2 Toxic or of doubtful value

- a Gold salts
- b Sulphur
- c Chaulmoogra oil
- d Arsenicals
- e Cinchophen and derivatives
- f Massive dose of vitamin products
- g Colchicine
- h Snake venom
- i Bee sting extracts, etc

on discharge Improvement was noted in a relatively larger percentage of patients treated for their focal infection than of the patients who had no focal infection

As we have stated previously we feel that treatment or removal of focal infection is important despite some opinions to the contrary We feel, in

addition, that in these chronic cases the time of focal removal and the method used are extremely important. In certain individuals one must proceed with the greatest caution lest he do more harm than good. We have been fortunate in this regard to have experienced no severe reactions. Finally, it is very important that one discriminates between infected and non-infected tissue before removal is attempted.

REST

Rest, both local and general, is necessary in the treatment of this disease. Nearly all these patients complain of early fatigue. The patients were instructed as to the proper amount of rest during each 24 hours. Activity must be kept within the limits of fatigue. The amount of bed rest is variable. In cases with hot swollen weight-bearing joints the bed rest should be absolute until the inflammation has subsided. This may be a period of weeks or months. The joints are carried through a painless range of motion several times daily. These rest periods are always carried out with the joints in the position of extension and function and maintained in that position by the necessary appliances. Later, graduated activity and exercise may be permitted. There is no one treatment directed to the joints as valuable as rest. With it the inflamed joints are kept motionless and the weight bearing and movement trauma entirely eliminated. It is often surprising how well these mentally and physically fatigued patients respond to bed rest. Naturally in some cases only minimal rest is desirable.

PHYSICAL THERAPY

Nearly all these patients received physical therapy. This includes heat of all types, light, massage, water, mechanical and electrical modalities and other physical agents. These valuable adjuncts to the treatment of atrophic arthritis will not be discussed as there is a wealth of available publications on this subject^{3, 15, 16, 17, 18, 19, 20, 21}. Our staff includes two competent physiotherapists who work under direct medical supervision. With portable equipment it is possible to treat patients at home as well as at the Clinic.

We have noted in this group little benefit derived from hyperpyrexia (induced by any means). We reserve its use to gonorrheal arthritis where it is extremely valuable^{22, 23}.

The judicious use of physical therapy is important. It requires judgment and direction of administration. When so used there appears to be no doubt as to its therapeutic effectiveness.

DIETOTHERAPY

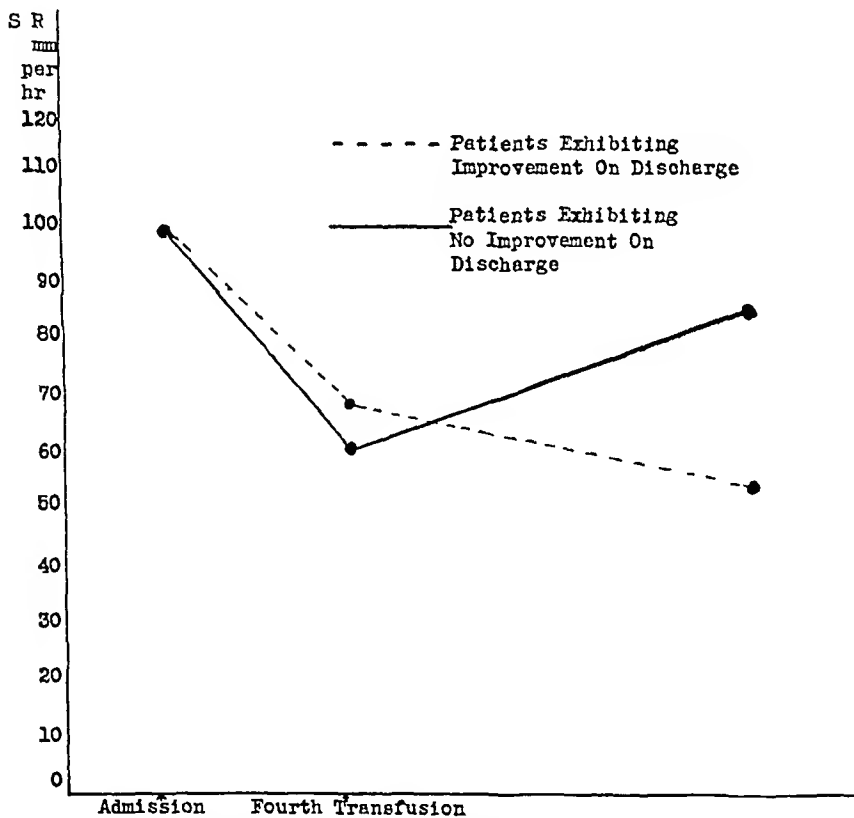
Much has been written concerning the value of diet in arthritis. Most of the patients in this study were underweight, hence they were placed upon a high vitamin, high calorie, low starch diet, supplemented when necessary (for weight gain) by milk and cream. Vitamin B was administered

routinely as wheat germ. This diet was varied occasionally to suit the needs of the individual patient. Obese patients were given the diet suggested by Pemberton⁸. It is remarkable how the doughy swelling responds to this latter diet. We have observed this same phenomenon to occur after starvation, nausea and vomiting, diarrhea and ether anesthesia. The significance of these observations has not been fully explained.

It is quite obvious that to secure constitutional improvement the underweight arthritic should gain weight, the obese arthritic should reduce. Although there are other factors concerned, dietary considerations are exceedingly important.

BLOOD TRANSFUSIONS

Blood transfusions have been extremely useful in the treatment of certain patients of this group. A total of 198 transfusions was given to 48



GRAPH 1 Showing the effect of blood transfusions upon the sedimentation rate
Sedimentation rate mm per hour (Westergren)

patients with an average of four transfusions per patient. The amount of blood given each time was from 300 to 600 c.c. or about 10 c.c. per kilo of body weight at two to six week intervals.

The effect of blood transfusions on the sedimentation rate is of interest (graph 1). It has been noted in the majority of the cases following a trans-

fusion that the sedimentation may drop to one half of its original rate. In this group this can not be accounted for solely by the improvement in the blood count. In addition, we have noted that in patients who improve the sedimentation rate following transfusions may fluctuate but the general progress is toward normal values, while in those who do not improve the sedimentation rate tends to rise toward its former level or even higher. In occasional cases the sedimentation rate may remain high even though the patient is clinically improved.

In this group receiving transfusions 66 per cent showed improvement on discharge. We do not favor blood transfusions in all cases but in certain individuals whose arthritis is particularly resistant to treatment and progressive, or who are markedly debilitated or have a persistent severe secondary anemia, transfusions are extremely valuable and should be utilized.

HELIO THERAPY AND CLIMATOTHERAPY

Nearly all arthritics of this type are benefited by a warm dry climate such as we have here in the southwest. It constitutes a valuable aid in the treatment of these patients who can spend a sufficient time in such a climate. It is equally true that a few are not benefited.

Heliotherapy was used in the treatment of the majority of these patients. Sun bathing was prescribed at a regular time, with duration and amount of exposure definitely indicated. There are a few contraindications to direct heliotherapy, namely, (1) the presence of fever, (2) the appearance of a general or local reaction and (3) complicating or debilitating conditions such as active tuberculosis, chronic myocardial disease, general debilitation and old age, etc. In febrile patients it is wise to give no direct heliotherapy but to utilize the indirect type. In case of a general or local reaction it is well to minimize the time of exposure, eliminate it entirely or to prescribe only indirect heliotherapy. We believe that both climate and sun are valuable agents in treatment.

LOCAL TREATMENT AND PREVENTION OF DEFORMITIES

Rest as noted above constituted an important phase of the treatment. Graduated bed rest, splinting and rest casts should be used not only at the onset but throughout the course of the disease. An arthritic joint is always a potential deformity and should be treated as such. Properly directed physical therapy is highly beneficial. Painful joints with limitation of motion and soft tissue swelling should be moved through the painless range of motion several times daily. Exercise and activity must be within limits of pain or fatigue. It is highly pleasing to note that patients can be treated throughout the course of their disease so that when activity has subsided these joints are functionally adequate—more pleasing perhaps when one realizes that, without adequate treatment over such a period, these same patients might become permanently disabled.

CORRECTION OF DEFORMITY

Because of the high incidence of deformities in these chronic cases their correction constitutes an important part of treatment. There are several non-operative methods available, namely, traction, cast wedging, turnbuckle and other adjustable splints and finally, manipulations with or without anesthesia. It seems very important that one proceed with utmost caution and with the dictum "do not harm." In addition, one must visualize as accurately as possible what the conditions will be a year or two years from the time of correction. It seems hardly necessary to mention that each joint should be studied extensively and other factors taken into consideration before correction is attempted. In our hands gentle, well-directed traction has been the method of choice. Occasionally we have found it necessary to resort to the other methods or even in some cases to discontinue correction because of a generalized or local reaction. Finally, it may be said that many deformities can not be completely corrected by non-operative methods and the procedure of choice should then be operative.

The operative treatment of deformity consists of synovectomy, arthroplasty, capsuloplasty, arthrotomy, osteotomy, arthrodesis, etc. It is well agreed that better results occur when the disease is quiescent. There are some indications, however, that these deformities may be corrected earlier, even during activity—in certain instances. Sufficient time has not elapsed to draw conclusion from our recent cases. It is worth emphasis that any corrective procedure should be preceded by an adequate period of preparation involving exercises, constitutional care and transfusions when indicated and followed by an equally persistent post-operative period of rehabilitation. If the disease is still active great care must be exercised to prevent recurrence of the deformity.

ANTIGENS AND VACCINES

As we have previously discussed vaccine and antigen therapy we will only mention again that we consider a patient suitable for vaccine or antigen when the sedimentation rate is high and the agglutination titers are low. Unfortunately there has been no diagnostic test of a reliable nature for determination of a patient's sensitivity to bacteria or bacterial products.

DRUGS

There has been a constant parade of drugs used in the treatment of arthritis. Among them may be mentioned cinchophen and derivatives, arsenicals, gold, sulphur, chaulmoogra oil, vitamin products, snake venom, colchicine and many others. There is no proof of their specific nature and there is evidence that severe toxic reactions may result from certain drugs—notably gold and cinchophen. At this Clinic we have found acetylsalicylic acid with or without some form of calcium or sodium bicarbonate

to be valuable. There are other non-toxic analgesics of acceptable value. Opiates are to be used with extreme caution and we have rarely resorted to them. Iron is of value in the accompanying anemia. It may be best given by the oral route in fairly large doses. Subcutaneous or intravenous administration of iron appears to have no advantages over the oral route and in some cases may be dangerous. There appears to be no advantage in giving salicylates intravenously as there is sufficient evidence to indicate that their irritative properties are central rather than local.

Sulphur and gold have been disappointing in our experience but we have noted some beneficial effect with massive doses of vitamin D².

RESULTS OF TREATMENT

It appeared worth while to correlate the time of treatment with the results. In addition, follow-up inquiries were sent to all of these patients to determine their progress since discharge. These follow-up reports came

TABLE V
Results and Duration of Treatment

Progress	Number of Patients	Per cent	Duration of Treatment
No improvement	35	12.82%	4.88 months
Slight improvement	28	10.68%	4.53 months
Moderate improvement	94	34.18%	7.95 months
Marked improvement	116	42.30%	8.20 months

TABLE VI
Results of Follow-Up Reports

	Number Reporting	Reported Condition 1-6 Years Later				
		Worse	Same	Improved	Well	Died
Patients showing slight or no improvement on discharge	21	9	8	3	1	
Patients showing moderate to marked improvement on discharge	87	9	18	30	28	2
Total	103	18	26	33	29	2

in after an elapsed interval of from one to six years and in most of the cases the elapsed time was longer than two years.

Out of this group of 273 patients 23.5 per cent or 63 patients exhibited little or no improvement during an average treatment period of 4.6 months. One to six years later follow-up reports on 21 patients of this group were as follows: nine were worse, eight remained the same, three were better

and one was well. The remaining 76.5 per cent or 210 patients exhibited moderate to marked improvement on discharge. Six per cent or 12 patients of this group were well when dismissed. The average duration of treatment was 8.1 months. Follow-up reports one to six years after discharge on 87 of these patients were as follows: 9 were worse, 18 were the same, 30 were improved, 28 well and 2 were dead.

These results indicate that of the 76 per cent of the patients treated who exhibited moderate to marked improvement on discharge, nearly all continued to improve in the years following. Some were entirely free from their arthritis and a few were worse. Out of the group (23 per cent) who showed no improvement nearly all were worse or the same, a few were better and only one was well. It is interesting to note that the average treatment time of those who exhibited moderate to marked improvement was eight months as compared to four months for those who showed little or no improvement. We feel that the length of treatment is an important factor. Patients should understand at the beginning of treatment that the course is long and will require not a few but many months of painstaking treatment. It is hoped that the time will come when we can treat this terrible disease throughout its entire course.

SUMMARY

Admission data on 343 cases of chronic atrophic arthritis may be briefly summarized as follows: (1) Chronic atrophic arthritis runs a more or less progressive course unless treated. (2) The percentage of these patients (60.06 per cent) who showed deformities is greater than that of patients who did not. (3) All ages and both sexes were affected, the females more frequently than the males and the highest incidence was in the third and fourth decades. (4) Focal infections were found in 57.73 per cent of these patients. In 80 per cent of these cases the foci were found alone or in combination from the respiratory tract up. Foci in the throat or pharynx were those most commonly observed, followed by foci in sinuses, gingival tissue, teeth and respiratory tract in their respective order. In the remaining 20 per cent of the cases there were infections of the urinary tract in one-half, and in the remaining cases, infections of the female pelvis, prostate, gall-bladder and colon, occurring in the order of frequency given. The organism most frequently found was a streptococcus of the hemolytic type.

The treatment of this disease involves a detailed plan embracing physical therapy, heliotherapy, dietotherapy, climatotherapy, treatment or removal of focal infections, rest both local and general, the prevention and correction of deformities, bacterial antigens and vaccines, mild analgesic and anti-anemic drugs and blood transfusions.

With such a plan 76.48 per cent of the patients treated were discharged moderately to markedly improved after an average treatment period of eight months. Of this group 6 per cent were entirely well. One to six years

later nearly all this group had maintained their improvement, or were well (33 per cent), and a few were worse. In the remaining 23.52 per cent of patients little or no improvement was noted on discharge after a treatment period of four months. Follow-up on these cases indicated that most of them were the same or worse while a few had improved. This indicates that treatment of arthritis involves many therapeutic factors which must be carried over a sufficient length of time before the maximum benefit can be derived. And, finally, that there is a certain percentage of patients who become worse or who are not benefited by treatment. It is the problems of this group particularly that should be the object of further research. Perhaps it is in this group that detailed study of the "soil" will give more information than the study of the "seed."

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TUMORS OF THE PULMONARY APICES AND ADJACENT REGIONS INVOLVING THE BRACHIAL PLEXUS *

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TUMORS which have their origin at the apices of the lung, or in the lower portion of the neck just above the clavicle, have aroused considerable interest in the past 13 years. A number of papers recently have appeared, including reports of cases that have been similar to those in the original group reported by Pancoast in 1924.

The tumors, Pancoast reported, occurred at the apices of the lungs and produced a characteristic group of clinical symptoms. Pancoast considered this type of tumor to be a distinct clinical entity and gave it the name, "superior sulcus tumor." In 1932 he reported four more cases. His criteria for diagnosis were (1) roentgenologic evidence of a new growth at the apex of the lung, (2) homolateral pain referred along the distribution of the involved nerves of the brachial plexus, (3) atrophy of the small muscles of the hand of the side affected, (4) early development of a homolateral Horner's syndrome, (5) roentgenologic evidence of destruction of adjacent ribs and vertebrae.

Pancoast first thought these tumors to be of pleural origin but later he considered that they might be branchiogenic, arising from the fifth branchial pouch. It may be noted, at this point, that several conditions may produce the symptom-complex of pain of the homolateral shoulder and arm and cervical sympathetic paralysis, such conditions are neoplasm of the spinal cord, meninges, or cervical vertebrae, or cervical ribs or trauma. Cervical sympathetic paralysis alone may be caused by tumors of the neck, aneurysm, enlarged lymph nodes, mediastinal neoplasm, tuberculosis, and trauma.

To date, 34 cases of this unusual syndrome have been reported, 26 more or less completely. It is interesting, however, that Hare, in 1838, in addition to describing a peculiar condition of the eye, which Horner later elaborated, also gave particulars of a "glandular scirrhus in a male", the picture closely paralleled that discussed here.

Excerpts from Hare's paper follow: "He had been attacked a month before with pain, tingling, and numbness along the course of the ulnar nerve of the left arm, which was most severe at the elbow, where there had also been some swelling and redness. There was, besides, pain through the left shoulder, extending across the chest to the opposite side, and upwards to the left eye and teeth of that side. The tongue was clean, appetite good, no cough or physical sign of pulmonary disease. After a

* Submitted for publication August 19, 1937

careful examination, the only cause that could be discovered to account for his symptoms was a small tumor, situated in the 'inferior triangular space' on the left side of the neck, which it was possible might be producing some pressure on the origins of the nerves going to form the brachial plexus

In addition to the foregoing symptoms the pupil of the left eye became contracted and the levator palpebrae ceased to perform its office "

Postmortem inspection revealed "a glandular scirrhus" at the base of the neck, which involved the major structures of that region, and extended downward into the superior mediastinum The pathology and the origin of the "scirrhus" were not recorded

This century-old report justifies the conclusion that tumors, whether primary in the cervical region, such as those arising from the fifth branchial pouch, or from the pulmonary apex, or metastatic cervical tumors, or neoplasms that infiltrate the cervical region from nearby structures will produce the characteristic group of symptoms and signs to which Pancoast called attention A brief review of the literature shows that in Pancoast's cases 6 and 7 the symptoms may have been caused by metastasis from a carcinoma of the uterine cervix The question of metastatic tumor may again be raised concerning the first case reported by Browder and DeVeer, while their fifth case was one of thymic carcinoma Frost and Wolpaw reported an instance in which a sympathoblastoma arising from the inferior cervical ganglion was the etiologic agent A squamous cell carcinoma of unknown origin was the cause of the "Pancoast syndrome," as reported by Graef and Steinberg

General agreement now exists that the symptoms presented by a primary apical tumor are far different from those expected from a neoplasm situated at the tracheal bifurcation Usually the symptoms of hilar tumor are cough, hemoptysis, recurrent attacks of fever and loss of weight If there is a history of unexplained pain in the thorax or shoulder, the lungs and cervical region should be carefully examined for tumor

To produce the Pancoast syndrome, the neoplasm must involve the brachial plexus, which has its origin in the fifth, sixth, seventh, and eighth cervical, and first thoracic segments of the spinal cord Lesions which affect the ulnar nerve, which arises from the eighth cervical and first thoracic segments and traverses the medial cord of the brachial plexus, will implicate the small muscles of the hand The sympathetic supply to the face and eye arises from the upper thoracic segments Horner's syndrome, in which there is paralysis of the dilator fibers to the iris and of the superior tarsal muscle, thus causing ptosis of the eyelid, and paralysis of Mueller's retro-orbital muscle, thus causing enophthalmos, is produced in the cases under discussion by neoplastic involvement of, or pressure on, the cervical sympathetic chain, which lies anterior to the cervical vertebrae Sweating is absent over the region of distribution of the affected nerves and a high cutaneous temperature and hyperemia are found in the same region

CASE REPORTS

Case 1 A white woman who presented many of the typical features of this syndrome, recently was observed at The Mayo Clinic. The patient was 64 years of age and was admitted with a history of dull, aching pain of six months' duration, the pain was in the left side of the thorax and extended to the left shoulder and arm. One year before her admission she had noted that her left eye was somewhat smaller than her right eye (figure 1). Diplopia had been present at intervals during this period. For six months she had noticed weakness, tingling and numbness of the left hand. She had lost 50 pounds (23 kg). Cough, bloody expectoration and fever were absent.



FIG 1 Horner's syndrome

Physical examination revealed left enophthalmos, narrowing of the palpebral fissure and unequal pupils, the right pupil was larger than the left. The ocular fundi were normal. The head was inclined to the right and the left supraclavicular fossa was fuller than the right. Left cervical and axillary lymph nodes were enlarged and firm. The thyroid gland was normal in size but the trachea was to the right of the midline. Laryngoscopy revealed normal vocal cords. Slight pulsation was present under the left clavicle.

Pulmonary percussion revealed left apical dullness. On auscultation, bronchial breathing, but no râles, were heard in the same region. The remainder of the pulmonary fields was clear and evidence of pleural fluid was absent.

Definite enlargement of the areas of dullness over the heart and great vessel dullness also were present. A loud, systolic murmur was audible at both the apical and aortic areas, this was accompanied by a thrill over the great vessels. Blood pressure, read on the right arm, was 110 mm of mercury systolic and 70 diastolic,



FIG 2 Shadow in left apical region

a reading could not be made on the left arm because of extreme hyperesthesia. The radial pulse was definitely stronger on the right.

Pelvic examination revealed a cystic mass on the right, about 8 cm in diameter, and this was considered benign.

The left interosseous muscles, the extensor muscles of the wrist and the biceps brachii were definitely weak. Examination of the blood disclosed moderate anemia and negative Kline, Kahn, Hinton, and Wassermann tests.

There was a large, radiopaque area in the left apical region, continuous with

the shadow of the great vessels (figure 2). Apparently the ribs or vertebrae were not involved by a neoplastic process. Definite thickening of the apical portion of the parietal pleura, extending to the fourth rib posteriorly, was seen under the roentgenoscope.

Necropsy was performed one day after the death of the patient and about 10 weeks after her dismissal from the clinic. The most striking pathologic change



FIG 3 Carcinoma of upper lobe of left lung and pleural implants

was that the upper lobe of the left lung was entirely replaced by a firm, white tumor which extended anteriorly over the pericardium and about 2 cm to the right of the median line (figure 3). The tumor also extended into the neck, lateral to the left lobe of the thyroid gland, where it invaded the left subclavian vein and brachial plexus. The bodies of the seventh cervical and first thoracic vertebrae were involved in the neoplastic process. The main tumor measured 17 by 17 by 15 cm. The cut surface was pinkish white, mottled with scattered yellowish areas of necrosis.

There was extensive metastasis to the pleurae of both lungs and to the hilar nodes. The liver also was the site of metastasis. Of further interest were calcareous changes in the aortic valve ring and a right parovarian cyst which had given rise to clinical physical signs. Terminal phenomena had consisted of severe cystitis, bronchopneumonia and left empyema. There was rather extensive chronic tuberculosis of nodes at the hilus of the lungs and there were tuberculous masses, apparently

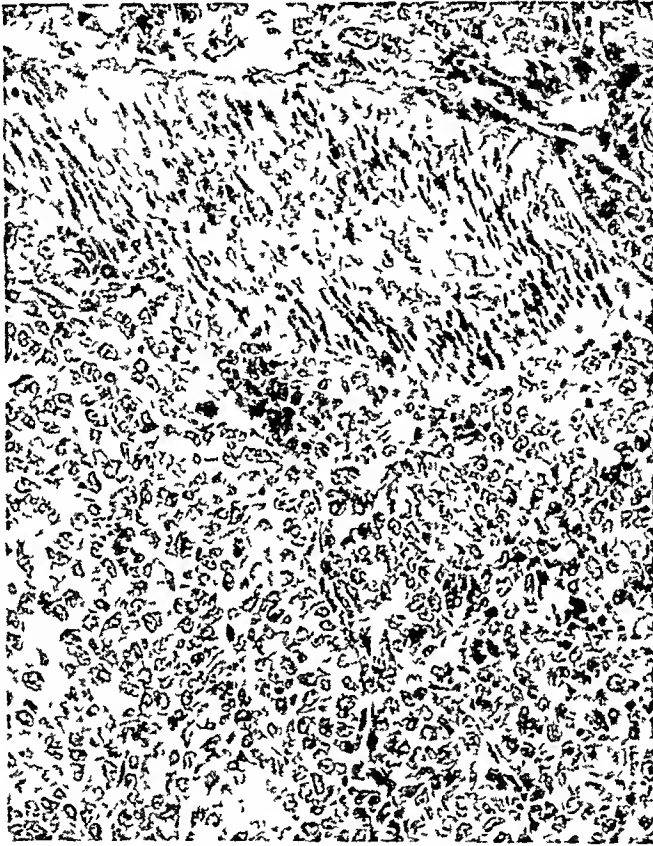


FIG 4 Nerve of brachial plexus invaded by carcinoma

quiescent, of the liver and spleen. Microscopically, the tumor was a squamous cell carcinoma. Figure 4 represents a section of the tumor as it involved the nerve bundles of the brachial plexus. Sympathetic nerve fibers also were involved.

Case 2 A second case which illustrates the point that any neoplastic involvement of the brachial plexus will produce the characteristic symptoms is that of a white man (figure 5), 61 years of age, who gave the following history. He had lost 60 pounds (27 kg) and considerable strength in about 10 months preceding his admission at the clinic. He had had moderate pain in the left lower part of the thorax, but cough or hemoptysis never had been present. The left pleural cavity has been aspirated 10 times in two months, the greatest amount of fluid obtained at any one time had been 84 ounces (2520 cc). The fluid was the color of honey and did not contain blood that could be detected macroscopically. Guinea-pigs had been inoculated to determine if the fluid contained acid-fast microorganisms, results had been negative. Four months prior to the time of admission the man had noted a somewhat tender, firm mass in the left side of the thorax. Pain in the

left elbow had been present at irregular intervals for three months and the left arm had become weak. There had been no numbness or tingling of the left upper extremity.

The patient was somewhat emaciated. The left pupil was slightly smaller than the right and enophthalmos, grade 1, was present. A large, solid mass extended from the left axilla to the crest of the left ilium. Resonance over the left lung was diminished, tactile fremitus was absent, and breath sounds were distant. The right pulmonary field was normal. Heart sounds were of fair quality and murmurs were



FIG 5 Appearance of patient and extent of lesion

not heard. The liver was enlarged so that it extended as far as the width of three fingers below the costal margin but the spleen was not palpable. The left axillary and the inguinal lymph nodes on both sides were enlarged and firm. On rectal examination, the nodes at the bifurcation of the aorta also were found to be enlarged. Moderate atrophy of the left interosseous muscles was present.

Stereoscopic roentgenograms of the thorax gave evidence of density throughout the lower two-thirds of the left lung, apparently without displacement of the heart or mediastinum. Very slight anemia was present but the sedimentation rate was

elevated to 60 mm per hour Examination of a stained blood smear did not disclose myeloid immaturity

Microscopic examination of a lymph node removed from the left axilla revealed the process to be an adenocarcinoma, grade 3 (figure 6)

In table 1, the majority of the completely reported cases are summarized Among other cases about which incomplete details are given are the fol-



FIG 6 Microscopic appearance of the left axillary lymph node

lowing Tobias reported four cases in which pulmonary neoplasm involved the brachial plexus The symptoms in another case he cited were owing to a metastatic tumor, the origin of which was the stomach Jacox cited a case of Fried, in which many of the features discussed were exhibited Steiner and Francis reported incompletely a case of a white woman, 62 years of age, who had thoracic pain owing to a medullary type of pulmonary carcinoma with involvement of ribs Lloyd, and Crile and Kearns made brief reference to the subject in their respective articles Guillion and Sterne, in addition to reviewing the literature, added a case of their own In their report they also give the details of a case of A Ricoldoni, who published six years before Pancoast's first contribution The report is incomplete, but an apical pulmonary tumor caused paralysis of the muscles innervated by the eighth cervical and first thoracic nerves Pain also was

TABLE I
Summary of Completely Reported Cases

Author	Age, Years	Sex	Duration of Symptoms	Chief Complaint	Wasting or Weakness of Muscles of Hand	Horner's Syndrome	Destruction of Rib	Situation of Tumor	Pathologic Characteristics	Necropsy Performed	Biopsy Performed
Pancoast	52	M	11 months	Pain	+	+	+	Left apex	Endothelioma, diffuse scirrhous carcinoma	0	+
	36	M	4 months	Pain	0	+	+	Left apex	Endothelioma	0	+
	60	M	Not stated	Pain	0	+	+	Right apex	Endothelioma	0	0
Henderson	59	M	6 months	Pain	0	0	0	Right apex	Endothelioma	0	0
	38	M	6 months	Pain	0	0	0	Right apex	Carcinoma of lung	0	0
	35	M	4 months	Pain	+	0	0	Left apex	New growth of lung	0	+
Pancoast	55	M	7 months	Pain	0	+	+	Right apex	Not stated	0	0
	62	M	8 months	Pain	0	+	+	Right apex	Not stated	0	0
	52	F	8 months	Swollen right arm	+	+	+	Left apex	Not stated	0	0
Jacov	32	F	2 months	Pain	+	+	+	Left apex	Not stated	0	0
	55	M	10 months	Pain	+	+	+	Right apex	Adenocarcinoma with scirrhous elements	+	+
	41	M	1 month	Pain	0	+	+	Left apex	Not stated	0	0

TABLE I—Continued

Fried ⁴	45	M	7 months	Pain	0	+	+	Left apex	Squamous cell carcinoma	+	0
Steiner and Francis	31	M	4 months	Pain	0	+	+	Left apex	Adenocarcinoma	+	0
	42	M	5 months	Pain	+	+	0	Right apex	Undifferentiated type of carcinoma	0	+
Clarke	53	M	*	*	*	*	+	Left apex	Epidermal carcinoma	+	0
	61	M	24 months	Pain	+	+	0	Left apex	Squamous cell carcinoma	+	0
Browder and DeVeer	57	M	Not stated	Pain	Not stated	+	0	Left apex	Medullary carcinoma	0	+
	62	M	9 months	Pain	+	+	+	Right apex	Squamous cell carcinoma	+	0
	62	M	7 months	Pain	Weakness of right upper extremity	Involve-ment of sympathetic plexus supply to face	+	Left apex	Squamous cell carcinoma	0	0
	46	M	4 months	Pain	+	+	+	Right apex	Squamous cell carcinoma	+	0
	35	M	2 months	Pain cough	0	+	0	Right apex	Thymic carcinoma	+	0
Frost and Wolpaw	38	M	4 months	Pain	+	+	+	Right apex	Symphoblastoma of inferior cervical ganglion	+	0
	54	M	24 months	Pain	+	+	+	Left apex	Squamous cell carcinoma	+	0
Grael and Steinberg	46	M	9 months	Pain	Not stated	+	0	Left apex	Squamous cell carcinoma	+	0
	47	M	6 months	Pain	+	+	+	Right apex	Alveolar carcinoma, squamous carcinoma unknown origin	+	0
Guillon and Sterne	55	M	2 months	Pain	+	+	0	Left apex	Not stated	0	0

* Patient presented clinical and roentgenologic findings in every way typical of those described by Pancoast

present over this area and a Horner's syndrome was found. Pulmonary signs were not present. Necropsy confirmed the clinical findings.

SUMMARY AND CONCLUSIONS

1 Two cases of Pancoast's "clinical syndrome" are presented and available published reports of cases are summarized.

2 Certain definite characteristics of these cases, owing to involvement of the brachial plexus are (a) pain in the thorax or the arm, or both, (b) cervical sympathetic paralysis, (c) weakness or atrophy of the muscles of the extremity affected.

3 Absence of a history of cough, hemoptysis, and recurrent chills and fever does not militate against a diagnosis of primary pulmonary neoplasm. This point is well illustrated by the first case cited.

4 In all cases in which there is obscure pain in the shoulder and in which other parts are negative to examination, roentgenologic examination of the thorax should be made, especially if evidence of cervical sympathetic paralysis is present. Pulmonary neoplasm is not to be immediately excluded because of lack of the usual symptoms.

5 Metastasis from tumors at any point in the body, if they involve the brachial plexus, will produce the characteristic chain of symptoms noted.

6 The available reported cases of this syndrome are briefly summarized.

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CIRCULATION TIME AS A DIAGNOSTIC AID IN HYPERTHYROIDISM *

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THE satisfactory results of present day treatment of hyperthyroidism make it essential that an accurate diagnosis be made before the late effects of the disease damage the heart and other viscera. The widespread use of basal metabolism equipment indicates the acceptance of this principle by the medical profession.

It is well known, however, that increased basal metabolism is not always synonymous with hyperthyroidism. There are a number of conditions which may at one time or another in their course exhibit such elevations in metabolism. This may be noted in heart failure, in some cases of hypertension, during the course of fevers, leukemia, polycythemia, and in certain emotional states with or without evidence of disturbance of the vegetative nervous system.

The converse, hyperthyroidism with normal basal metabolism, is more rarely met with. Nevertheless, genuine instances have been reported in which the basal metabolic rate has been normal throughout the entire course of the disease.¹ Likewise, the diagnosis in an otherwise typical case may be temporarily obscured by the effects of previous iodine therapy. These considerations indicate the need for other methods of approach, in evaluating the state of thyroid function, than a study of the metabolism alone.

The work of Hurxthal² and others has established the fact that the cholesterol content of the blood plasma bears a somewhat approximate inverse relationship to the degree of thyroid function. While this is not altogether reliable in the individual case, it is generally agreed that in myxedema the blood cholesterol is usually elevated, while in cases of severe hyperthyroidism, it is likely to be low. The wide range of normal values for blood cholesterol renders this method less useful in the border-line case.

About 10 years ago, Blumgart began his studies on the velocity of the blood flow. After developing suitable clinical methods for determining the speed of the circulating blood, he was able to demonstrate that there is a slowing of the pulmonary blood flow in myxedema and an increased rapidity of flow in thyrotoxicosis.³ The latter is reflected clinically in the increased pulse rate, pulse pressure, and stroke volume of the heart in hyperthyroidism. A partial explanation of the need for this increased blood flow is in the increased oxygen demands of the tissues in this disease. The red blood cells must be transported to and from the pulmonary capillaries with greater velocity in order to carry to the tissues the greater quantities of oxygen required. However, there appears to be an additional circulatory stimulant

* Received for publication August 24, 1937
From Medical Service No. 2 The Mount Sinai Hospital

in hyperthyroidism which is not present in other states of increased metabolism not of thyroid origin. The latter conditions show no change in circulation time.⁴

The lack of convenient and practical methods for determining the blood velocity delayed the general adoption of this procedure into clinical medicine. However, there have appeared a number of papers dealing with the circula-

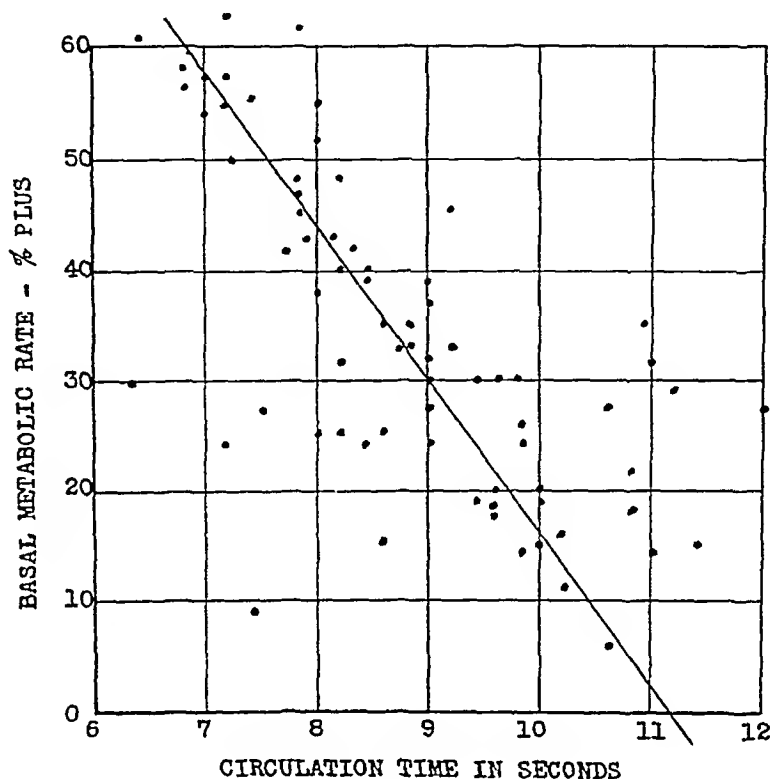


FIG 1

tion time in normal subjects, in patients with heart failure, and in instances of pulmonary disorders which might be confused with heart failure.⁵ Blumgart,³ Gargill,⁶ and Tarr, Oppenheimer and Sager⁶ have studied small groups of cases of thyroid disease from the point of view of the circulation time, and have been able to show that the circulating blood flow is more rapid in hyperthyroidism. When heart failure develops in such cases, the blood flow slows up, at first manifesting what appears to be normal velocity, and when the heart failure becomes progressively more severe, the readings approach those observed in heart failure from other causes. It is probable that slowing of the blood velocity is the earliest reliable sign of heart failure and often precedes the development of symptoms.

In a previous report, I described a simple clinical method for determining circulation time, employing calcium gluconate.⁷ The patient reclines, with the arm at the level of the right auricle, 2.5 c.c. of 20 per cent calcium

gluconate solution,* or 5 c c of 10 per cent solution, are injected into a vein at the elbow as rapidly as possible through an 18 gauge needle. The end point is that moment at which the patient first experiences an intense sensation of heat in the mouth and tongue. The term circulation time indicates the time required from the arm to the tongue (the moment of injection to

COMPARISON OF BASAL METABOLIC RATE, BLOOD CHOLESTEROL, AND CIRCULATION TIME IN PATIENTS WITH HYPERTHYROIDISM

Case No	Sex	Age	Average B M R %	Cholesterol	Circ Time	Remarks
1	F	39	plus 30	148 mg	9 0 sec	
2	F	47	18	170	9 6	
3	F	21	57		6 8	
4	F	45	33		9 2	Toxic adenoma
5	M	28	40	154	8 4	
6	F	39	55	138	8 0	
7	F	29	55		7 2	
8	F	40	15	200	10 0	Recurrence
9	F	37	18		10 8	
10	M	39	35	142	8 6	
11	M	39	46	134	9 2	Acromegaly present
12	F	41	63		7 2	
13	F	51	22		10 8	
14	F	18	25	180	8 0	
15	F	26	52		8 0	
16	F	40	62	95	7 8	Died before operation
17	F	19	48	177	8 2	
18	F	42	14		11 0	
19	M	18	27	148	10 6	
20	F	19	9	169	7 4	Iodine therapy
21	M	59	25		8 6	
22	F	46	35		8 8	
23	M	44	27		9 0	
24	F	40	15		11 4	Postoperative
25	F	23	25	160	8 2	Toxic adenoma
26	F	19	56	133	7 4	
27	M	35	42		7 7	
28	M	54	19		10 0	
29	F	39	32	134	11 0	Heart disease
30	F	19	30	142	6 3	
31	F	18	24	187	7 2	
32	M	40	57	129	7 0	
33	M	65	35	146	10 9	Rheum heart dis
34	F	—	43		7 9	
35	M	39	11		10 2	
36	F	60	24	190	9 8	
37	F	29	58	140	6 8	
38	M	42	26	150	9 8	
39	M	36	38		8 0	

the moment of perception). This corresponds to the path traversed by the material through the peripheral venous circuit, through the lungs, to the left heart and finally to the first peripheral arterial capillary bed off the arch of the aorta, where it is perceived as a sensation of heat in the mouth. It

* Neocalglucon 20 per cent solution, supplied through the courtesy of the Sandoz Chemical Works, Inc

should be measured accurately with a stop watch. The sensation descends rapidly downward, following the path of the arterial circulation. In more than 500 patients observed during the past two years, we have found this method accurate, practical and safe. There have been no accidents, no important subjective discomfort, no venous thrombosis, and no sloughs.

COMPARISON OF BASAL METABOLIC RATE, BLOOD CHOLESTEROL, AND CIRCULATION TIME IN PATIENTS WITH HYPERTHYROIDISM—*Continued*

Case No	Sex	Age	Average B M R %	Cholesterol	Circ Time	Remarks
40	M	40	plus 6	252 mg	10.6 sec	Iodine therapy
41	F	38	57		7.2	
42	F	31	47		7.8	
43	F	42	39	163	9.0	Rheum heart dis
44	M	33	30	170	9.4	
45	F	22	48		7.8	
46	F	45	50	140	7.2	
47	F	29	20	168	9.6	
48	F	42	33	200	8.7	Toxic adenoma
49	F	40	39		8.4	
50	F	—	43		8.1	
51	F	24	33	139	8.8	
52	M	24	40		8.2	
53	F	53	29	210	11.2	Toxic adenoma
54	F	53	37	122	9.0	
55	M	41	27		12.0	Liver enlarged
56	F	36	42		8.3	
57	F	34	15	130	8.6	Recurrence
58	F	35	45	135	7.8	
59	F	58	32		8.2	
60	F	36	30	154	9.6	
61	F	—	14		9.8	Iodine therapy
62	M	23	16	198	10.2	Mild symptoms
63	F	33	54		7.0	
64	F	18	32		9.0	
65	F	40	30		9.8	Early heart failure
66	F	36	61	250	6.4	
67	F	39	20		10.0	Thyroid overdosage
68	M	29	24	151	8.4	Thyroid overdosage
69	F	30	19		9.4	Toxic adenoma
70	F	24	18	208	9.6	Toxic adenoma
71	F	22	27		7.5	
72	F	40	24		9.0	

Average Circulation Time of 72 cases 8.8 ± 0.9 seconds

In our previous report, we established the normal arm to tongue circulation time in 60 patients to range from 10 to 16 seconds, with an average normal of 12.5 ± 1.0 seconds. These tests were not performed under basal conditions, but a short period of rest in the reclining posture was required. It was found that the pulse rate did not influence the circulation time, as cases of paroxysmal tachycardia showed normal blood velocity, but that, in common with metabolism tests, it was occasionally affected by emotional states, particularly apprehension. Under these circumstances, the reading may be verified on the following day. Normal circulation speed was found

in hypertension, bronchial asthma, nephritis with edema, and in well compensated valvular heart lesions. The circulation time was shorter in hyperthyroidism, fever and anemia and was prolonged in heart failure and in myxedema.

Including the 17 cases previously reported, we now present circulation time studies in 72 cases of hyperthyroidism. Most of these patients were being prepared for operation and the diagnosis was later proved histologically. Some were observed in the office at the time metabolism tests were being made. All patients were carefully studied clinically and by repeated metabolism tests. In many instances, cholesterol estimations were made. The average circulation time for the 72 cases was found to be 88 ± 0.9 seconds, the variation being from 6.3 to 12.0 seconds. The latter reading was encountered in a patient with severe muscular weakness, and an enlargement of the liver that could not be definitely attributed to heart failure. It should be remembered, however, that a relative slowing of the circulation in a patient with hyperthyroidism of long duration should always arouse a suspicion of latent or beginning heart failure. In the accompanying table, we have indicated the average of the two highest metabolism readings, as the circulation time tests were not always done on admission. In many instances, they were not performed until after the patient had begun preoperative iodine medication. Cholesterol determinations are also shown for comparison. In the accompanying graph, correlation points have been plotted indicating the circulation time and basal metabolic rate. It will be noted that the values for circulation time and basal metabolism follow a definite trend and that the distribution of the majority does not depart widely from the mean. It would appear on the basis of this evidence that a shortening of the circulation time is characteristic of hyperthyroidism, and that there is a definite relation between the rapidity of the blood flow and the height of the metabolism in this disease.

We have also demonstrated to our satisfaction, although we cannot present the evidence here, that conditions other than hyperthyroidism which give an increased rate of metabolism are associated with normal circulation time. In following some of our thyrotoxic patients after operation, a return to normal of the circulation time has been observed. In two cases, mild myxedema developed some months after operation, and the blood flow became correspondingly slowed.

Patient 20 was admitted, having received iodine medication before coming to the hospital. Basal metabolic rate on the following day was plus 9 per cent. A circulation time reading of 7.4 seconds strongly supported the original diagnosis of hyperthyroidism. Any doubt as to the correct diagnosis was dispelled by the rising metabolism after iodine had been temporarily discontinued, by the development of a postoperative thyrotoxic crisis, and subsequent histologic study of the thyroid gland.

SUMMARY

The calcium gluconate method of determining circulation time was employed in 72 patients with hyperthyroidism. The average rate was found to be 8.8 ± 0.9 seconds, as contrasted with an average reading of 12.5 ± 1.0 seconds in 60 normal subjects. Evidence is presented to indicate that the circulation time test is useful in the diagnosis of hyperthyroidism. The test is accurate, simple to perform, and entirely safe, as indicated by an experience of more than 500 patients with various clinical conditions. It is suggested, furthermore, that a consideration of the circulation time and blood cholesterol in addition to the conventional basal metabolism test affords a more accurate and balanced interpretation of the state of thyroid function than dependence on one method alone.

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THERAPEUTIC EXPERIENCES WITH COBRA VENOM^{*}

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INTRODUCTION

THE materia medica of the ancients abounded in preparations taken from the animal world. Primitive physicians believed that the organs, secretions and excretions of all kinds of animals, including man, possessed mysterious medicinal virtues. Such animal preparations therefore figured largely in the materia medica not only of the Egyptian, Assyrian and Babylonian but also of the Greek and Latin periods and continued to flourish in the pharmacopoeia of the Dark Ages. Even after the Renaissance, at the dawn of modern medicine, the old dispensatories and pharmacopoeias listed a surprisingly large number of "preparations" derived from the animal world. To make them more impressive they were appended to these preparations such Greek, Latin and Hebrew names as appear, for instance, in the Pharmacopoeia Londinensis or New London Dispensatory of William Salmon, Professor of Physick (London, 1702). When the era of modern rational therapeutics and experimental pharmacology had begun, however, most of these preparations were dropped from materia medica but in the past two decades the medicinal use of animal products has been revived to a great extent, largely on account of the developments in the science of endocrinology and the discovery of the vitamins.

Serpents, however, have retained a place of honor in all materia medica from time immemorial. In recent years snake venoms have become the subject of both experimental laboratory and controlled clinical investigation. Their therapeutic uses fall into three distinct categories. One group of venoms, composed mostly of the *Crotalidae* or rattlesnake family, has been used empirically in epilepsy. A second group of snake venoms has been employed in connection with the treatment of blood diseases and used particularly for the control of hemorrhage. In this group are included the American moccasin, *Ancistrodon piscivorus*, the tiger snake, *Notechis scutatus*, and the tropical serpent, *Viper russellii*. But by far the most interesting group from the standpoint of pharmacology and therapeutics is the venoms of the cobras. These have received the greater amount of experimental scientific attention and their therapeutic applications are also of major importance.

It is interesting to note that in the year 1929 an American physician, the former Adolph Monaesler of New York City, gave the first impetus to the study of cobra venom. This wealthy physician, who traveled extensively,

^{*} Read before the annual meeting of the American Therapeutic Society in Atlantic City, N. J., June 4, 1937.

became interested in the curious case of a Cuban leper who, instead of succumbing to the bite of a poisonous tropical spider, was relieved of the excruciating pains in his arm from which he had long been a sufferer. This observation suggested to Monaelesser the possibility that some animal poisons might serve as pain-relieving agents and he communicated his thoughts on this subject to Calmette, distinguished savant of the Pasteur Institute who, far from ridiculing the idea, thought it worth putting to a test. Monaelesser in collaboration with the French physicians, Oliveira and Dumatias, began an examination of snake poisons. The three physicians finally selected for their special study the venom of the cobra probably because it is richest in those substances to which the name of "neurotoxins" has been applied. These substances, the chemical nature of which is still unknown, exert their poisonous effects on the nervous system. The results the French investigators obtained in their studies with cobra venom read like a fairy tale but cannot be recounted here in detail. Suffice it to say that the scientists of the Pasteur Institute finally reported that injections of small and safe dosages of cobra venom effectively relieved severe pain of chronic character and particularly that of advanced and hopelessly malignant tumors. In concluding these introductory remarks, the writer desires to mention the interesting fact that 800 years ago the famous Hebrew physician and philosopher, Maimonides, the prototype of the physician in Scott's novel, "The Talisman," stated in his medical treatise, *Pirque Moshch* (ed. Vilna, 1914, chap. 9, p. 26) that snake venoms were useful in the treatment of *tza-ra-ath*, or "leprosy," and *sar-ton*, or "cancer."

COBRA VENOM AS AN ANALGESIC

Cobra venom was thus first scientifically employed by scientists of the Pasteur Institute, who found it useful in relieving the severe pains of malignant diseases. A number of well-known names are connected with this work and the literature on the subject has been given by the writer in another paper.¹ Stimulated by the reports, the present author began both laboratory and clinical investigation of the drug. In investigating this subject, the writer's object was fourfold: he wished (1) to study the pharmacology and toxicology of cobra venom according to the latest technical methods, (2) to prepare and assay biologically a sterile and safe solution of cobra venom for therapeutic use in human patients, (3) to ascertain in carefully controlled studies how effectively cobra venom alleviates the severe pain of patients with malignant tumors, and (4) to analyze the pharmacodynamic mechanism by which the drug produces analgesia or relief of pain, as described by previous writers.

The author performed most of his experiments with the venom of the Indian cobra, *Naja tripudians*, sent him in the form of dried scales by a colleague in India. Additional experiments were made with the venom of the African cobra, *Naja haji*, obtained from another colleague in Egypt. It

may be stated at once that the venom from both species acted in the same way. In connection with clinical studies of cobra venom it was very difficult at first to devise a method by which solutions of the drug could be absolutely sterilized from both aerobic and anaerobic organisms. Inasmuch as most snake venoms are easily destroyed by high temperatures and soon commence to deteriorate even at room temperature, special methods had to be employed in making the solution of cobra venom. Finally, however, there was developed in our laboratory a technic whereby a safe solution of the drug can be prepared.

The writer has devoted considerable study to the mechanism of the analgesia produced by cobra venom, a subject which he discussed in a previous paper and which had heretofore received little attention.² Some think that because that member of a human victim which has been struck by the fang of the cobra becomes numb and paralyzed, the venom produces a local anesthetic action. This is true when an enormous quantity of venom is injected at one place. Such a numbness, however, is in reality a manifestation of protoplasmic poison and not, in the strictly pharmacological sense, an evidence of the local anesthetic effect produced on the peripheral nervous structures. The writer has definitely established by his experiments that such minute quantities of cobra venom as have been employed therapeutically in very dilute concentrations, produce no demonstrable local anesthetic action either on the sensory or motor nerve endings or on the nerve fibers of the ascending or descending peripheral nervous system. On the contrary, all the writer's physiological or pharmacological data, derived from experiments performed in different ways, point to the pain areas in the cerebrum as the locus of the analgesia produced by injections of cobra venom. Evidence to support this conclusion has been adduced from (1) experiments concerning the antipyretic effect produced by cobra venom, (2) studies on the antagonism displayed by cobra venom for certain drugs producing epileptiform convulsions in animals, (3) experimental psychological study of the behavior of white rats trained in a circular maze, (4) special quantitative studies on pain threshold of guinea pigs and (5) special quantitative studies on pain threshold of human beings according to methods developed by the writer in connection with his study of opium alkaloids^{3, 4, 5}

The conclusion drawn from the various experiments was that cobra venom, like opium and its principal alkaloid, morphine, relieves pain through its action on the higher centers of the brain. The two drugs exhibited a marked difference, however, with regard to what may be styled the "fourth dimension of pharmacodynamics," namely, the time element involved in all pharmacological action.⁶ It was found that while morphine relieves pain very promptly—that is, that the analgesia it produces is rapid in onset—the effect of the alkaloid wears off within a few hours. Cobra venom, on the contrary, does not induce analgesia rapidly. It is usually necessary to give an injection of the drug on each of several successive days before the analgesic action is fully developed. The analgesia effected by this drug, how-

ever, once it is induced, lasts much longer than that of morphine. In a separate paper the writer has described biochemical experiments which revealed that morphine is rapidly oxidized by fresh brain tissue *in vitro* and by the oxidative processes of the brain *in vivo*, whereas cobra venom remains unchanged in the brain tissue of animals injected therewith for a much longer time⁷ and its therapeutic action is therefore of longer duration.

CLINICAL EXPERIENCES

The usual dosage of cobra venom recommended by the writer is five mouse units. A mouse unit is the quantity of cobra venom solution required to kill a white mouse weighing 22 grams within 18 hours after its intraperitoneal injection with the drug. Foreign investigators have employed much larger doses,⁸ but the writer deems it wiser to begin with small therapeutic doses and to study each clinical case carefully before the optimum dosage for the individual patient is established. Five mouse units is a dose below the average and certainly quite innocuous. Cobra venom is not as poisonous as some well known alkaloids and even less toxic than the glucoside ouabain, which is generally regarded as but a heart stimulant⁹. Of course, there is no difference between drug and poison. Every drug may under certain conditions become a poison and, *vice versa*, almost every poison may occasionally become a useful medicinal agent. It is the writer's usual procedure to first inject but one half the contents of an ampule, or 2½ mouse units. On the following day, a whole cubic centimeter (5 mouse units) is injected. Similar doses of 5 mouse units each are injected for several successive days until a definite analgesia is noted or a contraindication for the use of the drug is encountered. In the writer's experience the latter sequel is very rare. Once analgesia has been established, patients may usually be kept comfortable with two or three injections of 5 mouse units each a week. The writer has personally administered two such injections twice a week to patients with advanced and hopelessly malignant cancers for months in succession and been able to keep them comfortable by using no other drug than cobra venom.

The injections are given intramuscularly. Local reactions have been unimportant.

In the subjoined table are classified the pathological conditions in which cobra venom has been employed by various physicians in collaboration with the writer. He is especially grateful for the cooperation of Dr. Curtis F. Burnam of the Howard A. Kelly Hospital, who was one of the first and most interested collaborators in the work, and also for the continued interest of the late Dr. Joseph Colt Bloodgood of the Johns Hopkins Hospital in this connection. The clinical studies reported here have been carried on for several years and the writer is unable to name the numerous colleagues who have so kindly reported their experiences to him.

TABLE SHOWING CLASSIFICATION OF CASES

Cancer of breast	20	Cancer of ovaries	4	Cancer of stomach	2
Cancer of uterus	35	Cancer of tongue	5	Cancer of orbit	1
Cancer of rectum	13	Cancer of floor of mouth	3	Myxolipoma	1
Cancer of jaw	13	Cancer of primary glands	5	Intestinal adhesions	1
Cancer of bladder	7	Cancer of prostate	5	Pyelocystitis	1
Cancer of retroperitoneal tissue	6	Cancer of penis	1	Raynaud's disease	1
Cancer of lungs and mediastinum	6	Cancer of spine	5	Angina pectoris	2
Tumor of bone	5	Cancer of thyroid	2	Arthritis	10
Epithelioma	4	Cancer of tonsils	2	Tic douloureux	6
Cancer of Fallopian tubes	1	Cancer of antrum	1	Other neuralgias	10
		Cancer of larynx	1	Morphinism	3
		Cancer of intestines	3	Parkinson's disease	15
Total number of cases studied					200

Of the 185 cases enumerated in the table (15 cases will be discussed separately), 70 per cent showed definite relief of pain and in 10 per cent more of the cases some slight relief of pain was manifested. Twenty per cent of the total number either experienced no relief at all or were doubtful. One half the 70 per cent of patients that were definitely relieved showed marked improvement in their general condition and could dispense with other medication. The series of cases reported here is larger than that discussed for the first time before the National Academy of Sciences, and the therapeutic results obtained agree admirably with those described by Professor Saenz of the Pasteur Institute, who wrote the author as follows:

Monsieur et Cher Confrere. En ce qui concerne le traitement du cancer par le venin de cobra, un fait est desormais acquis: il a une reelle action anesthesiante dans 70 pour cent des cas traites. Nous ne pouvons pas dire le même chose au sujet de son action curative car malheureusement les cas studies sont peu nombreux et ne permettent jusqu'a present d'aucune conclusion.

It will be noted that Professor Saenz claimed that 70 per cent of his cases experienced relief or "anesthesia" and that he adds that cobra venom is but a symptomatic therapeutic agent and not a curative drug although studies on the effects of venoms on experimental tumors in lower animals are in progress in European laboratories.

Similar experiences have been described by Kirschen,¹⁰ who summarizes his findings as follows:

Cobra venom injections were given 23 patients suffering from inoperable and incurable carcinoma of the gastrointestinal organs. There were 15 stomach cases, three lung cases, three intestinal cases and two breast carcinomata. The effect of treatment in most cases was to reduce pain and improve the general condition of the patient. Improvement in general condition and increase in strength were ascribed to control of pain. Morphine was reduced to a minimum and appetite was restored so that patients could take nourishment, in that way their wasting was checked. The analgesia, followed by no narcotic by-effect or mental depression, undoubtedly exerted a favorable psychological influence on the patients. The author states in conclusion that he would dislike to miss a single opportunity to use cobra venom in the treatment of inoperable and recurrent cancer and agrees with Korbler with regard to the therapeutic results obtained with this drug.

It would require too much space to describe in detail here all the cases which have been collected by the writer or to note the impressions concerning cobra venom treatment sent in by various physicians, but a few citations on this subject may be appropriate. The following interesting account is taken from a letter written by a colleague in the middle West who was originally very skeptical regarding the analgesic virtues of cobra venom.

Patient has been in a hospital for far-advanced cancer patients for one year—carcinoma of the cervix with recto-vaginal fistula. She has had considerable pain about the rectum which was not relieved by an alcohol intraspinal injection done several months ago. We had given her narcotics twice to the point of addiction, then took her off them. But they had soon again to be given in increasing quantities. Just before March 6, 1937, she received morphine ($\frac{1}{2}$ gr) and dilaudid ($\frac{1}{16}$ gr) every two hours, and she was quite nervous, irascible and hard to handle. For several months her appetite was poor and all her vegetables and other food had to be strained twice before she would touch them. Though she had rectal incontinence, she seemed constipated and her abdomen was tense.

Snake venom was started March 6. One half an ampule was given the first day and then one ampule a day for five days, after that the drug was given every other day until she had had six more injections. Not much effect was noticed until about five injections had been given but since then she has been a different person. The narcotics were gradually lessened so that now she receives a grain or $\frac{1}{2}$ grain of codein at night and nothing else. She has had no snake venom injections for six days now. Her appetite has improved, so that now she eats anything and the nurses, and the director in charge, asked me to express to you their gratitude especially because they do not have to laboriously prepare all her food.

The subjoined lines from a resident physician of an eastern hospital indicate the efficacy of cobra venom solution in relieving pain caused by bone affections.

You will recall that some time ago you sent me 10 ampules (5 mouse units) of cobra venom with the request that I use it as an analgesic in cases of intractable pain. Thus far, I have been unable to use it on cases of coronary thrombosis, as you suggested, but have succeeded in prevailing upon our surgeon-in-chief to permit me to use it in the case of one of our graduate nurses who has an adamantinoma of the jaw with secondary staphylococcal infection, producing an osteomyelitis. In her case opiates (morphia, pantopon, dilaudid, etc.) had very little, if any, effect in alleviating the severe pain accompanying her condition, and it was because of this that Dr. ——— permitted the house staff to use the cobra venom. Our results with it have been nothing less than remarkable, and I feel that you should know about them.

After a preliminary dose of 25 mouse units, she received 5 units daily for two days. At the end of this time she became rather stuporous, so that cobra venom was discontinued for three days. Then it was begun again in doses of 25 mouse units (0.5 cc), and she has been receiving this dosage every two days. It has relieved her pain almost entirely, and for the first time in her clinical course of almost a year here at the hospital, she has had sedation and rest. No narcotics have been given in conjunction with the cobra venom. At night she receives nembutal, from 15 to 30 grains, and this has been sufficient recently to induce sound sleep.

Again, a physician on the Pacific coast, who has used many ampules of cobra venom solution, states that the drug has proved highly satisfactory in the treatment of cancer cases suffering much pain.

In cancer patients the relief has been highly satisfactory, and the injections have not apparently been required oftener than every two to four days, an average of about three days

In severe arthritis—chronic hypertrophic and atrophic—the results have been fully as good as “one could expect” In all persons there was surcease from mental depression, which relief lasted from two to five or six days

The following excerpt is taken from the letter of a Canadian physician who treated a confrere for advanced carcinoma of the rectum This case was remarkable in that the patient survived for many months, kept comfortable by regular injections of cobra venom solution

We are pleased to advise you as to the progress of the case of Dr S—— Prior to the injection of cobra venom he was receiving as much as 4 H M C's number one with quarter grain of morphia added at times He received the first ampule of cobra venom February 19 with no untoward effects noted This was repeated the following day and again on the 21st During the first few days we had to resort to narcotics only occasionally By the third day his relief from pain was almost absolute Since his third injection there has been complete and lasting disappearance of his previously excruciating pain It was observed that for a few days following the third injection he lost his sense of taste, this, however, has returned

The subjoined report concerns one of the unfortunate sequelae of radiation treatment in cases of malignant disease This patient had a cancer of the roof of the mouth and was vigorously treated with radium, which caused complete disappearance of the malignant tumor but resulted in a persistent and extremely painful ulcer on the same surface The patient's son, himself a physician, describes the results of cobra venom therapy as follows

May I begin by saying that I can never thank you enough for the cobra venom you sent me for my father I would have reported my results to you before this had not my father's condition been very poor for some time following the sudden death of my mother However, at the present writing he is almost his old self again He was in my office today, having driven himself in from the country, a distance of about 16 miles (incidentally, to have a plate adjusted by the dentist) His condition had so markedly improved after the first 11 injections of cobra venom that when he received in addition two more doses from the last lot you sent, all pain subsided and I saw no need to give him any more The ulcer in the roof of his mouth has completely healed but has left an opening through the hard palate Practically all tenderness has vanished so that he can wear a plate made to cover the opening with much comfort There are no signs of any malignancy and I feel that he has almost completely recovered, anyway, his improvement appears to continue

While cobra venom was chiefly advocated in cases of hopelessly advanced malignant tumors and their metastases, the writer during the past year or two has become interested in extending its use to the treatment of certain non-malignant conditions Included among these are severe neuralgias like tic douloureux, cases of chronic arthritis which could not be relieved except by narcotics, and cases of angina pectoris with subacute, long-lasting paroxysms of pain The number of arthritis cases treated with this drug is

still not large enough to warrant discussion although considerable relief of pain has been obtained in some instances

Finally, the writer wishes to add a word as to a new indication for therapy with cobra venom. While he was studying a series of chronic arthritis cases and endeavoring to relieve their sufferings with various non-narcotic drugs, two patients afflicted with advanced Parkinson's disease with contractures and severe arthritic pains came under his observation through the courtesy of a colleague. It was deemed advisable to try the effect of cobra venom (in place of a host of antipyretics and codeine, to which they had become accustomed) on these two patients. To the surprise of attending physicians, cobra venom not only relieved the pain but also relaxed the rigidity of the muscles and produced a general amelioration of the patients' symptoms. This finding prompted a search for cases of Parkinson's disease, particularly those with marked pain and rigidity. Fifteen such cases have already been studied and it may be stated that the spasticity and pain of half that number have been definitely relieved. The number of cases thus treated is still too small to warrant any general conclusion but certainly stimulates further study on the subject.*

The *modus operandi* of the drug in such cases is probably a complex one (1) The analgesic action of cobra venom certainly plays a rôle, (2) the anticonvulsant property of the drug may play a rôle, and (3) it is quite probable that certain peripheral effects of cobra venom described by Ciccardi¹¹ may also be involved in the mechanism of the drug's action.

It is well to call attention to the fact that practically all the cases tabulated above had been treated, prior to administration of cobra venom, with all kinds of drugs including such narcotics as morphine, codeine, pantopon and dilaudid and in many cases had also been subjected to radiation with roentgen-rays and with radium. Very often cobra venom was used as a last resort when all the other therapeutic measures had failed, and it is gratifying to be able to state that in most of such cases the narcotics and other analgesic drugs were gradually reduced in dosage and finally dispensed with altogether after initiation of the cobra venom treatment.

The question of addiction arising at this point in his discussion, the writer wishes to state that up to the present time no signs of addiction, in the narcotic sense of the word, have been noted after as much as a year's treatment with cobra venom. Some physicians, however, have reported that their patients' mental attitude in general had been favorably affected by the drug. Whether this effect of cobra venom therapy is a true euphoria or merely the result of relief from pain and improvement in general condition

* Since the manuscript of this paper was sent the editor, the use of cobra venom in Parkinson's disease has been further investigated by the writer and other physicians. Such studies have confirmed the original findings concerning effectiveness of the drug in relieving symptoms of the Parkinsonian syndrome. The most important work done in this direction has been reported by Drs. Gavle and Williams in the February issue of the Southern Medical Journal, 1938.

of the patient cannot be definitely asserted. In the series he has studied only three cases of true morphine addiction have been brought to the writer's attention. One of these, a physician who suffered from neuritis, became an addict to morphine and dilaudid and came to a Baltimore hospital for treatment. Without the patient's knowledge, the dosage of the opiate was gradually decreased and cobra venom injections were substituted for such therapy. Finally the patient was taken off narcotics altogether and kept comfortable with the cobra venom injections. An out-of-town physician has reported that he has successfully treated two morphine addicts by combining injections of cobra venom with those of insulin. The drug has so far been found to produce no such symptom as morphine or other opiates or cocaine effects. In some cases it has been found to produce a general stimulation and improvement of the patients' psyche probably through relief of pain.

SUMMARY

The venom of the deadly cobra, in sufficiently small doses and in sterile solution, has been found to be an efficient therapeutic agent for the relief of pain, particularly that of advanced malignant disease. Its use is being extended to the treatment of certain chronic non-malignant diseases accompanied by a great deal of pain. This drug, which is no more poisonous than many of the alkaloids and glucosides officially recognized by the medical profession, has been successfully used to displace analgesic drugs of the coal-tar and narcotic types. Like morphine, it depresses pain areas in the cerebrum but it differs from morphine in that its analgesia is slower in onset and longer in duration than that effected by the alkaloid. Modern pharmacology and therapeutics have thus restored the old empirical use of snake venoms described by the ancients to a place in the armamentarium of the progressive physician of today.

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GASTRIC SECRETION IN CASES OF PERNICIOUS ANEMIA *

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MANY authors believe that achlorhydria is a constant finding in cases of pernicious anemia. There are, however, a number of reported cases of pernicious anemia in which free hydrochloric acid was present in the gastric contents. Alsted was able to collect 32 such cases from the literature.

The cause of the achlorhydria in these cases is unknown. Faber was of the opinion that achlorhydria is always the result of atrophic gastritis which, according to him, is a constant finding in cases of pernicious anemia. Hurst, on the other hand, emphasized the constitutional factor in achlorhydria. The frequent familial occurrence of achlorhydria and of pernicious anemia, together with Conner's observation that achlorhydria has a distinct tendency to occur frequently among blood relatives of patients who have pernicious anemia, supports this view. It was Hurst's opinion that the absence of free hydrochloric acid predisposes to the development of inflammation of the mucous membrane.

There has been much evidence produced to prove that achlorhydria usually, if not always, precedes the onset of the anemia by a considerable time. Riley, Conner, Strandell, Levine and Ladd, Hurst, Faber and Gram, and Sturtevant have reported cases in which achlorhydria was found from one to several years prior to the onset of symptoms of pernicious anemia. In Strandell's series of 20 cases there was only one case in which free hydrochloric acid was found to be present before the development of pernicious anemia.

We have reviewed the records of 906 consecutive cases from the files of The Mayo Clinic, in which a definite diagnosis of pernicious anemia was made. Achlorhydria was found in all of the cases. This finding corresponds with the recent report of Sturgis on 600 cases of pernicious anemia. In none of our cases was there a return of free hydrochloric acid following treatment for the anemia. This finding is in contrast with that of Hurst, who has observed four cases of pernicious anemia in which the secretion of free hydrochloric acid returned following treatment of the gastritis. However, treatment for gastritis was not instituted in any of the cases we reviewed. Jones, Benedict and Hampton have demonstrated improvement in the appearance of the gastric mucous membrane during treatment of pernicious anemia.

In 36 of the cases a study of the gastric secretion was made from two to 21 years prior to the onset of symptoms of pernicious anemia. In the majority of these cases the concentration of hemoglobin was determined.

* Submitted for publication May 10, 1937

and a blood count was made at the time of the first examination. The findings are recorded in table 1. Those cases in which an analysis of the gastric contents was made in the two years before the first appearance of

TABLE I
Clinical Findings in Cases of Pernicious Anemia

Case	Age of Patient at Time of First Examination, Years	Sex	Percentage of Hemoglobin (Dare)	Corpuscles per Cubic Millimeter of Blood		Free HCl in Gastric Contents (Method of Topfer)	Years Which Elapsed Between Original Examination and Development of Symptoms of Pernicious Anemia
				Erythrocytes	Leukocytes		
1	42	F				0	20
2	59	F	73	4,440,000	7,000	0	10
3	29	F	71	4,950,000	7,800	0	21
4	54	F	82		5,700	0	5
5	37	M	79	4,670,000	7,300	0	11
6	42	M	81	4,380,000	8,400	0	3
7	34	M	78	4,980,000	7,900	0	10
8	51	F	70	4,250,000	6,700	0	7
9	46	F	76	4,040,000	6,300	0	9
10	57	M	75	4,280,000	6,500	0	8
11	55	M	70			0	3
12	68	M	70	3,870,000	7,500	0	5
13	44	M	85	5,120,000	6,400	0	13
14	53	F	80	4,180,000	7,100	0	17
15	49	M	79			0	18
16	54	M	75			0	10
17	39	M	74	4,030,000	7,500	0	6
18	39	F				0	21
19	58	M	75	4,590,000	4,500	0	5
20	65	M	75	4,130,000	7,700	0	2
21	55	M	71	4,270,000	5,500	0	11
22	30	M	81	4,680,000	9,400	0	11
23	65	F	75	4,760,000	7,000	0	11
24	44	F	78	4,430,000	6,300	0	5
25	55	M	80	4,780,000	6,800	0	4
26	48	F	65	4,730,000	5,700	0	5
27	41	F				0	16
28	54	F	62	3,880,000	5,000	0	3
29	65	M	80	4,010,000	6,400	0	3
30	35	F	73	4,460,000	8,800	0	10
31	56	F	84	4,980,000	6,200	0	12
32	46	M	85		8,900	34	19
33	41	M	70	4,230,000	6,700	0	12
34	37	F	84	4,440,000	6,400	0	12
35	41	F	70	4,470,000		16	17
36	54	M		4,460,000		0	2

symptoms of pernicious anemia were purposely excluded. In the last column of table 1 is recorded the number of years which elapsed between the first examination of the gastric contents and the onset of symptoms of

pernicious anemia Only cases in which a clear-cut history of the onset of pernicious anemia could be obtained are included

From a study of these cases it appears that in 34 cases achlorhydria was present from two to 21 years before the first symptoms of pernicious anemia developed, and in two cases (cases 32 and 35) free hydrochloric acid could be demonstrated 19 and 17 years, respectively, prior to the onset of pernicious anemia

The average age of the patients at the time of the original examination was 48 years According to the figures of Vanzant, Alvarez, Eusterman, Dunn, and Berkson, about 18 per cent of normal individuals of a corresponding age group have achlorhydria

It appears from these observations that achlorhydria almost always can be found a number of years prior to the development of the first symptoms of pernicious anemia, and we are in complete agreement with the statement made by Strandell, namely, that achylia in pernicious anemia is not a symptom due to the anemia but a factor of a far more deep-seated character

It is noteworthy that in this group there are only two cases with achlorhydria (cases 26 and 28) in which microcytic hypochromic anemia was present prior to the development of pernicious anemia In the remaining 34 cases the values for hemoglobin and the number of erythrocytes varied within the normal range at the time of the original analysis of the gastric contents

A relationship between simple achlorhydric anemia and pernicious anemia has been suggested by the finding of achlorhydria in the two diseases Heath, for instance, has reported a family in which some members suffered from hypochromic anemia whereas others had typical symptoms of pernicious anemia Cases in which a transition of simple achlorhydric anemia into pernicious anemia occurred have been reported by Witts, Faber and Gram and others Faber and Gram said that "there is such a close relationship between these two diseases that we have grounds for assuming a very intimate pathogenetic connection" It seems to us that the occasional occurrence of these two diseases can be explained on the basis of coincidence, and the fact that in the present group of cases only two such instances could be found makes us believe that the two diseases form definite clinical entities

SUMMARY

Achlorhydria was a constant finding in a series of 906 cases of pernicious anemia In 36 cases analysis of the gastric contents was performed from two to 21 years prior to the onset of symptoms of pernicious anemia In 34 of these cases achlorhydria was found In two cases free hydrochloric acid could be demonstrated 19 and 17 years before symptoms of pernicious anemia developed In only two cases was a hypochromic anemia found at the time of the original examination We believe that pernicious anemia and simple achlorhydric anemia are separate clinical entities

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URTICARIA—A NEW THERAPEUTIC APPROACH ~

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URTICARIA is a localized and circumscribed edema of the skin due to contraction and distorted osmotic balance in the superficial capillaries of the cutis. It has long been considered to be an allergic manifestation, but anyone who has dealt with chronic urticaria has encountered the refractive cases which in spite of all types of allergic withdrawals and desensitizations, will respond to no therapeutic measure. A number of cases are reported in the literature that have continued for many years without relief. Evaluating the allergic factor in the problem is unusually difficult, as this type of case gives the poorest response and is most inaccurate as far as skin tests are concerned, group diets, leukopenic indices, and patch tests are often of no avail. It has seemed to us that this problem of altered vessel permeability, plus a localized edema, could be approached, as in the treatment of other types of edema, from the purely chemical point of view. This, of course, has been done for many years with the use of ammonium chloride, hydrochloric acid, etc., but with the recent work on the sodium-potassium relationship in edema, it occurred to us that this might be an effective therapeutic approach. A review of the recent literature on potassium metabolism and the results obtained in a small series of patients have seemed to bear out this assumption.

The proportion of inorganic salts in blood serum is sodium 100, potassium 6.1, calcium 2.7, and magnesium 0.8. Normal serum contains from 320 to 350 mg. per cent of sodium and 18 to 22 mg. per cent of potassium. Many experiments have shown that deficiency of potassium induced in growing animals causes a definite stunting and if long continued results in death. Feng¹ reproduced Adrian's experiment and showed that the skin-muscle preparation of the frog, when scraped, loses its tactile excitability. He was able to prove that this loss was due to liberation of potassium from the cells of the skin, if the potassium was washed away the skin irritability returned. He was then able to show that application of potassium to an uninjured skin preparation had the same depressing effect on excitability. Duhre and Horton² have also demonstrated that potassium ions have the same depressant effect on muscle excitability. That is to say, when a skin-muscle preparation is irritated nature pours out an excessive amount of potassium to ease the local irritability, and the same effect may be produced artificially by application of potassium to an isolated segment. Nathan and Stern³ in their studies of calcium and potassium content of serum in patients with various types of skin disease found that in the acute dermatoses the potassium fell to a subnormal level, and returned to normal as the skin lesions im-

* Read at the St. Louis meeting of The American College of Physicians, April 22, 1937.
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proved Mathison⁴ showed that intravenous injection of potassium caused a primary fall in the blood pressure with a secondary rise, and that intra-arterial injection caused a marked primary rise. McGuigan and Higgins,⁵ repeating his experiment, found that potassium had the same action when injected by either route if preceded by epinephrin. Epinephrin increased the potassium in the blood serum, it caused vaso-constriction, contraction of smooth muscle, and cardiac depression. The site of action is directly on the peripheral arterial musculature, and an increase in serum potassium is necessary before the hypertensive effect is obtained. Many other investigators have shown that potassium produces a rise in blood pressure. D'Silva,⁶ and also Schwartz⁷ have noted that epinephrin causes an increase in the serum potassium. Camp and Higgins⁸ have definitely shown that potassium has two actions on the heart: first, vagus stimulation, and second, an increase in ventricular irritability identical with that due to epinephrin. All of the potassium salts apparently cause this effect except potassium permanganate. The potassium threshold is always increased by epinephrin. Schwartz found an increase of 86 per cent in serum calcium following epinephrin. In all experiments potassium and epinephrin acted identically on the heart, intestines, bronchioles, kidneys, etc. One function of the adrenal gland is to maintain a constant potassium content of tissue, and when the epinephrin secretion stops, potassium accumulates in the tissue. Effects attributed to epinephrin are *actually* the effects produced by potassium migration which epinephrin causes. Camp and Higgins, in their explanation of the adrenalin reaction are quoted as follows: "Changes effected by adrenalin are actually produced by potassium. Adrenalin causes an increase in serum potassium. Potassium salts injected intravenously effect changes identical with those produced by adrenalin. This is true not only for the cardiovascular system but for the intestine, bladder, etc. This effect occurs after the removal of the adrenals. Potassium also produces fleeting hyperglycemia, but if potassium is present in large amounts the blood sugar is low."

Klauder and Brown,⁹ in their work on the calcium-potassium ratio and the alteration of cutaneous irritability in rabbits have shown that there is a direct relationship between the degree of irritability and the amount of serum potassium. When the serum potassium was increased, the irritability of the skin was increased. *This is directly compatible with Feng's original experiment, that is, when the serum potassium is high it is because the utilizable potassium has been taken into the serum at the expense of the skin, and the skin irritability, therefore, is increased because it lacks the high potassium content in the cutaneous tissue which decreases its irritability.*

Many investigations have shown that there is a release of histamine in the skin in urticaria. Alexander,¹⁰ and others have noted that if a given area is repeatedly stimulated eventually there will be no response to the histamine stimulation. This can be accounted for on the basis of Feng's work as follows: After repeated stimulation potassium is mobilized in the

given area and the irritability is finally suppressed by the increase in the skin potassium in this area

Because of these basic facts it seems logical, therefore, that potassium should be a valuable drug in the treatment of edematous lesions of the skin for two reasons: first it lowers the skin irritability directly, and secondly, its pharmacological reaction is very similar to and definitely allied with epinephrin

Results in the small series of patients that we are reporting are far from conclusive, but definitely indicate the therapeutic response. All of these patients had been tried on the various allergic regimes and orthodox treatment without success.

CASE REPORTS

Case 1 D. J., white, male, aged 42. History of recurrent attacks of urticaria for 13 years. Physical examination and laboratory studies were negative. Skin tests were negative. Rowe diets gave no relief. Calcium lactate, nitrohydrochloric acid and ephedrin compounds were not helpful. On April 28, 1936, he was put on a high protein, low sodium, acid-ash diet with ammonium chloride, 45 gr daily, and potassium chloride 60 gr daily. In 24 hours the hives had cleared entirely and he has remained free ever since. He remained on a strict diet for eight weeks when citrus fruits were added. Discharged 15 weeks after institution of treatment on regular diet, entirely recovered.

Case 2 R. B., white, male, aged 57. Recurring urticaria of 10 years' duration. Skin tests were negative. Had had no relief from all types of allergic diets, acid regimes, ephedrin, etc. Had noticed on many occasions recurrent urticaria after taking milk of magnesia (this alkali apparently altering the calcium-potassium ratio). On the outlined regime he has had only an occasional hive and states that his skin has been better than for the previous 10 years.

Case 3 N. M., white, female, aged 60. Urticaria of four months' duration, no allergic history except migraine in mother's family. General physical examination and laboratory work were entirely negative. Various group diets were tried for four weeks without relief. Large doses of nitrohydrochloric acid and ammonium chloride caused little change. Skin tests showed a number of three and four plus reactions, but the removal of these offending foods made no change in the course of the urticaria. On April 7, 1936, patient was put on a low salt regime and nitrohydrochloric acid continued. Her next visit was five weeks later when she stated she was greatly improved but still having an occasional lesion. At this time she was put on a high protein, low sodium, acid-ash diet with 90 gr of potassium chloride daily and has remained comparatively symptom-free since that time.

Case 4 R. L., white, female, aged 40. Has had hives all her life, severe for two and a half years. Has been under the care of a number of dermatologists and has taken vaccines, cleared up foci of infection and taken various types of diet without relief. Skin tests were inaccurate because of a general dermatographia. This patient had a mild secondary anemia and a mild hypochlorhydria. She was put on a high protein, low sodium, acid-ash diet and the following is an excerpt from a letter written four weeks after leaving the hospital:

"I have made a decided improvement. Feeling generally better for longer than I can remember. I still have slight itching. Last night I ate soup with a tiny bit of salt. I had hives at 10 o'clock. Had some recurrence when I ran out of the potassium chloride."

Case 5 B S, white, female, aged 18 Chronic urticaria, recurrent for two years and a loss of 25 pounds in weight Recurrence of hives whenever she had a cold Various types of diet gave no relief No history of allergy in family Physical examination and laboratory work were entirely negative Was put directly on a high protein, low sodium, acid-ash diet with added vitamin D and 60 gr of potassium chloride daily Four days later she had very few hives and at the end of 15 days the hives had cleared entirely Skin has remained clear except for an occasional dietary indiscretion When last seen she was taking a fairly full general diet with simply a low sodium content

Case 6 N F, white, female (through courtesy of Dr Francis E Sultzman) This patient was an obese, mildly hypertensive, hypopituitary type of individual who had been on a low caloric diet for weight reduction In November 1936, she developed a severe urticaria After this had been present for one month she was put on a high protein, low sodium, acid-ash diet and the urticaria cleared up promptly, until at the end of 10 days she was entirely free from all signs and symptoms There has never been any recurrence She has remained on alternating low caloric, low sodium, acid-ash diet alternating at two week intervals with regular diet

This series of patients was observed from a purely clinical standpoint, laboratory facilities were not available for the many chemical determinations necessary to make the study complete However, all of the patients responded clinically in a manner that was most gratifying The high protein, low sodium, acid-ash diet with added potassium chloride as outlined by Baiker¹¹ for the relief of cardiovascular edema, and as recommended by Rusk and Newman¹² in the treatment of portal cirrhosis with ascites was devised to maintain a constant mild diuresis This is accomplished by mild tubular irritation which the potassium produces and by the additional fluid loss which an acid-ash residue causes Proteins, non-citrus fruits, and certain vegetables catabolize to such a residue From this regime there results a shift in the mineral balance of the tissue fluids, with an increase in the potassium constituents at the expense of the sodium We have employed this diet, which follows below, in two forms one a well balanced menu of normal caloric value for those in average nutritional states, the other, of low caloric (1050 cals) figures for those patients who are obese

HIGH PROTEIN, LOW SODIUM, ACID-ASH DIET OF AVERAGE CALORIC VALUE

FRUITS

3 servings daily, fresh or stewed, but should include either prunes, plums, cranberries, or currants once daily

VEGETABLES

2 large servings daily, especially beets, carrots, brussels sprouts, yellow corn, kohlrabi, lettuce, mushrooms, peas, spinach, kidney beans, parsnips

MEAT

2 servings daily

EGGS

2

MILK

1 glass

CREAM

½ glass

BUTTER

Salt-free, 6 squares

CEREAL

Oatmeal or wheatena, Farina, puffed wheat or rice occasionally

BREAD

Graham bread, 3 large slices or 6 small slices daily

RICE, MACARONI OR SPAGHETTI

1 serving daily

POTATO

1 serving

JELLY, PRESERVES OR HONEY

2 level tablespoons

SUGAR

Ad libitum—at least 1 tablespoonful

NOTES

All foods are to be prepared without salt and no salt is to be served with meals
 Potassium chloride (from 2 to 5 gm in shaker) may be given as salt substitute
 Spices—cinnamon, sage, paprika, pepper, cloves, nutmeg, allspice may be used
 Small servings of citrus fruits may be added after fluid volume is established
 Additional vitamin D to be supplied

Coffee or tea, 1 cup daily

HIGH PROTEIN, LOW SODIUM, ACID-ASH DIET OF LOW CALORIC VALUE
 (APPROXIMATELY 1050 CALORIES)

BREAKFAST

1 serving of 10 per cent fruit

2 eggs

1 slice whole wheat bread $3\frac{1}{2}$ by $2\frac{5}{8}$ by $\frac{1}{2}$ "

Coffee with saccharin and 2 tablespoons skimmed milk if desired

LUNCH

Veal cutlet one piece 6" by 4" by $\frac{1}{2}$ ", or

2 veal chops, or

Lean round steak one piece 4" by 3" by $\frac{3}{4}$ ", or $\frac{2}{3}$ cup ground lean beef, or $\frac{2}{3}$ cup sweetbreads, orCalf liver $4\frac{1}{2}$ slices 2" by 3" by $\frac{1}{4}$ ", or

3 pair frog legs—large, or

 $1\frac{1}{2}$ pieces fish 4" by 3" by $\frac{1}{2}$ "

Broil these meats with mineral oil

Vegetables

1 serving of 5 per cent vegetables

Salads

1 Hard cooked egg (1)

2 Cottage Cheese— $\frac{1}{4}$ cup3 Vegetable salad of 5 per cent vegetables If this salad is selected, add $\frac{3}{4}$ cup broth to this meal

Serve salad on 3 lettuce leaves with mineral oil dressing

Make this dressing by using your favorite French or mayonnaise
 recipe, substituting mineral oil for salad or olive oil,
 and potassium chloride for table salt

1 serving of 10 per cent fruit

 $\frac{1}{4}$ cup skimmed milk or skimmed buttermilk

DINNER

- $\frac{3}{4}$ cup broth or jellied broth
- Roast veal, lean beef, chicken, turkey, or lamb $2\frac{1}{2}$ slices
4" by 4" by $\frac{1}{8}$ "
- 1 serving of 5 per cent vegetables
- Vegetable salad of 5 per cent vegetables with 3 lettuce leaves and mineral oil dressing
- 1 serving of 10 per cent fruit
- $\frac{3}{4}$ cup skimmed milk or skimmed buttermilk

DIET INSTRUCTIONS

- 1 Eat nothing that is not on diet list
- 2 Do not use citrus fruit oftener than once daily, best to omit entirely
- 3 Do not use fats in cooking Mineral oil may be used
- 4 Do not use table salt in cooking or on food
- 5 Do not take any alkaline medicine as sodium bicarbonate
- 6 Limit fluid to 7 cups, $\frac{3}{4}$ full, daily, including liquids consumed with meals

The problem of potassium toxicity to which older investigators attach much importance has not been a complication in this series. Only in one patient, an anemic, emaciated individual have we noted muscular pains, vertigo, headache, sweating, and other symptoms of potassium intoxication. These were quickly relieved by a reduction in dosage. Potassium chloride in doses of 60 to 90 grains a day has been a safe drug in our hands, more readily tolerated if enteric coated.

COMMENT

The potassium-sodium-adrenal relationship is already a definitely established clinical entity in Addison's disease¹³. A sound physiologic and pharmacologic basis seems to exist for the treatment of the various allergic phenomena by further change in the already abnormally altered mineral balance. It has been definitely shown from numerous sources that in skin irritability and skin inflammation the potassium metabolism is markedly altered, and that an increase in skin potassium causes an appreciable decrease in localized irritability. It also has been shown definitely and conclusively, that potassium is almost identically adrenal-like in its pharmacological action. Because of these known facts it seems logical that certain allergic problems could be approached from this therapeutic angle with benefit. In a small series of cases of chronic urticaria, a high protein, low sodium, acid-ash diet, with added potassium chloride, has produced promising clinical results. We hope that this small series of cases will stimulate a further trial of what we believe to be a sound and fundamental therapeutic principle.

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UPPER LOBE PNEUMONIA IN THE ADULT

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PNEUMONIA of the upper lobes is neither a new nor a rare occurrence. It was described by Laennec and also by his contemporaries, Andral and Broussais. However, despite the common knowledge of its existence there have been exceedingly few references to this subject in the literature. This is equally true of the standard textbooks which deal very extensively with the general subject of pneumonia. It is not difficult to fathom the cause of this apparent neglect. The diagnosis of apical pneumonia by physical signs, alone, is attended with great difficulty and, in the absence of routine roentgenograms, the number of cases diagnosed correctly is very small and has offered little opportunity for clinical study. We have therefore made a detailed analysis of a series of cases of upper lobe pneumonia at the City Hospital with particular emphasis on the differential diagnosis, the course of the illness, and the prognosis. We hope that by calling attention to this type of pneumonic involvement the diagnosis will suggest itself in many obscure pneumonias observed in private practice without physical signs of consolidation.

As was stated above upper lobe pneumonia is by no means a rare occurrence, it is only the diagnosis which is infrequent. In a series of 522 cases of pneumonia Adams¹ found 97 instances (18.5 per cent) of isolated upper lobe involvement. MacCordick,² in a similar series, reported a 26 per cent incidence and Warr and Alperin³ found a 10 per cent incidence. Our study covered a period of 21 months from August 1934 to April 1936. The total number of pneumonia cases admitted to the Second Medical Service was 180 of which 24 (13.3 per cent) had primary upper lobe involvement. There were 20 white patients and 4 colored ones and the sex incidence was 18 males and 6 females. The age groups ranged from the second to the ninth decade but the majority of the cases (70 per cent) were in the third, fourth, and fifth decades.

Three types of onset were noted, namely, acute, catarrhal, and meningitic. The first two groups included the vast majority of patients and consisted of 22 cases. There were but two instances of frank meningitic onset. Of the nine cases whose illness began acutely with chill, fever, and chest pain there were two which subsequently showed meningitic features. The catarrhal group consisted of 13 patients. All began with upper respiratory disease. Four developed pneumonia insidiously, seven had acute symptoms following the catarrhal phase, and two showed meningitic manifestations after the catarrhal period.

* Received for publication October 9, 1936.

From the Second Medical Service of the City Hospital, New York.

The course of the illness in these 24 upper lobe pneumonia patients was carefully analyzed. The degree of toxicity was arbitrarily divided into three grades according to the composite clinical appearance of the patients and it was found that sixteen (66 per cent) of the cases were in Grade III (markedly toxic), four (17 per cent) were in Grade II (moderately toxic), and four (17 per cent) were in Grade I (slightly toxic). The number of patients who required oxygen therapy is also an indication of toxicity inasmuch as the routine requisites for oxygen administration were a heart rate above 135, respirations above 35, or the presence of cyanosis. Eleven patients were given oxygen. The extent and type of pyrexia were also noted. There were 20 patients with temperature above 102° F. Of these 11 were continuously high, seven were remittent, and two were intermittent. There were four patients with temperatures below 102° F, two were continuous and two were remittent.

Study of the lobe involvement of these cases according to roentgen-ray findings revealed 14 instances of single upper lobe pneumonia and 10 instances in combination with either the contra-lateral upper lobe or one of the lower lobes. The number of times each individual lobe was affected was as follows:

Lobe	Number of Instances Involved
Right upper	19
Right middle	1
Right lower	4
Left upper	7
Left lower	6
Right and left upper combined	2

It is of interest that in three of the cases of single upper lobe involvement no physical signs could be detected despite the roentgen demonstration of the lesions. In the cases with multiple lobe involvement the diagnosis of associated lower lobe disease by physical signs checked very closely with the roentgen-ray. The course of illness in the two groups was strikingly different. The 14 cases with single lobe involvement had a mortality rate of 21 per cent whereas the 10 cases with multiple involvement had a mortality rate of 70 per cent.

The duration of illness in the entire group of upper lobe pneumonias varied considerably. Of the 14 cases which survived five recovered by crisis and nine by lysis. The chart below depicts the number of days of illness of each of the patients and the mode of termination of the disease.

The number of cases in our series is not large enough to warrant any generalized conclusions but the above chart definitely shows that most of the patients who died did so within a 10 day period of illness. It also indicates that most of the patients who recovered by lysis were ill for a period greater than 10 days. These facts suggest that in view of the high mor-

DURATION OF ILLNESS AND MODE OF TERMINATION

	Number of Patients	Individual Duration of Illness (in days)	Average Duration of Illness (in days)
Terminated in Crisis	5	6 6, 6, 9, 9	7 2
Terminated in Lysis	9	4, 7, 11, 16, 16, 16, 18, 22, 24	14 9
Terminated in Death	10	4, 4, 5, 5, 7, 9, 9, 10, 11, 22	8 6

ality rate (42 per cent) in this disease a 10 day period of survival may be of some prognostic significance. In considering the condition of the pneumonic lesion in the patients who recovered there was found no instance of unresolved pneumonia in the entire group. The roentgenograms of nine showed complete disappearance of the lesion and the remaining six showed residua such as thickening of the apical and interlobar pleurae or linear fibrosis. There is a strong possibility that if these six cases had been roentgen-rayed again they also would have shown complete absorption of the infiltration. This contention is somewhat strengthened by the fact that most of them had no roentgenograms within a week of discharge. None of the patients who recovered had any physical signs at the time they left the hospital.

Most of the cases were worked up completely from the laboratory standpoint and particular emphasis was given to examination of the sputum for tubercle bacilli. There was no instance in which tubercle bacilli were found. In 20 of the cases the sputum was typed for pneumococci by the Neufeld method. The results were as follows:

Number of cases negative Types I-XXXII	13
Number of cases positive Type I	3
Number of cases positive Type II	2
Number of cases positive Type III	1
Number of cases positive Type XIV	1

There may be some significance in the high percentage of negative typings as this is in marked contrast to the results usually obtained in typing lower lobe pneumonias.

Examination of the urine in 20 cases showed nine instances of albuminuria, three instances of hematuria, two instances of glycosuria (non-diabetic), and one instance of choluria. Seventeen cases had chemical examinations of the blood. Two showed azotemia, two showed hyperglycemia (non-diabetic), and three showed cholemia. Twenty-two patients had blood Wassermanns of which two were positive. One of these recovered with complete resolution. Blood counts were done routinely on admission and when indicated during the course of illness. The figures showed nothing of particular significance. The range of leukocytosis was from 10,000 to 35,000 and the percentage of polymorphonuclear cells varied

from 45 to 95 All cases showed a decided shift to the left by the Schilling count

No pulmonary complications were observed However, there were many extra-pulmonary complications which were indicative of the severity of the disease Five patients showed toxic psychoses, nine had toxic albuminuria, three had focal glomerular nephritis of whom two showed azotemia, three had toxic hepatitis The severity of apical pneumonia particularly in regard to prostration and cerebral symptoms has been pointed out by Norris and Landis ⁴

The treatment of these cases was chiefly supportive with great emphasis on fluid intake Oxygen was administered when necessary One case was given serum The inability to obtain a specific typing of the sputum in the majority of the cases was responsible for the lack of a more general use of serum therapy

In discussing the differential diagnosis of apical pneumonia it is of considerable interest that ten (42 per cent) of the cases were diagnosed as pulmonary tuberculosis on admission The physical signs of many of the cases, particularly those with beginning resolution, were identical with those found in tuberculous lesions The history of acute onset with chest pain, chill, and fever, when present, was of some diagnostic value but considerable significance was attached to the presence of labial herpes which is rarely, if ever, seen with pulmonary tuberculosis The roentgen-ray was the most valuable diagnostic aid While lobar consolidations may occur in tuberculosis they do not undergo complete resolution within a period of two weeks as do those in pneumonia Putrid lung abscess may resemble apical pneumonia at the onset both clinically and radiographically but the diagnosis is usually established with the expectoration of foul sputum Meningitis must also be included in the differential diagnosis Six of our patients showed meningitic symptoms and in two of them spinal punctures were performed because of frank meningitic signs In these latter two instances there were neither pulmonary symptoms nor signs on admission In a report of six cases of apical pneumonia Lepage ⁵ noted that three of his patients had no cough or expectoration at the onset

Five of our patients were admitted with the diagnosis of pneumonia based on symptoms alone No physical signs could be elicited over the affected areas despite their demonstration by roentgen-ray Two of these cases showed physical signs during the resolution phase but the other three showed no signs on daily examinations throughout the entire period of illness In these latter instances the diagnosis was made possible only by the roentgenograms These facts strongly suggest the possibility that the numerous cases observed in private practice in which the patients have the typical history and symptoms of pneumonia but no physical signs are instances of upper lobe involvement

The clinical syndrome of apical pneumonia with rapid and complete resolution of the lesion is depicted in the following case reports

CASE REPORTS

Case 1 M H, a 16 year old girl, was admitted on March 12, 1936, with a history of productive cough, evening rise in temperature, and night sweats of two weeks' duration. On physical examination the patient did not appear acutely ill. There



FIG 1 (3-13-36) *Case 1* Pneumonic consolidation of right upper lobe, small infiltration in right middle lobe. Left side negative.

were dullness and diminished breathing over both upper lobes. The temperature ranged between 99° and 102° F. The sputum was negative for tubercle bacilli and for pneumococci types I-XXXII. The admission diagnosis was bilateral upper lobe pulmonary tuberculosis. Pneumonia was considered only as a possibility. Roentgen-ray examination on March 13 showed a pneumonic consolidation of the right upper lobe and a small infiltration in the right middle lobe. The left lung was negative (figure 1). The clinical course was uneventful and the temperature subsided gradually. Daily physical examinations revealed no signs of resolution at any time but

a roentgenogram on March 24 showed complete clearing of the lesion except for a few fibrotic strands extending from the hilum and a thickening of the interlobar pleura (figure 2)

Case 2 L M, a 32 year old woman, was admitted on February 17, 1936, with a history of fever and pain in the right chest of four days' duration. She had noticed progressive loss of weight and weakness for several weeks prior to the onset of the

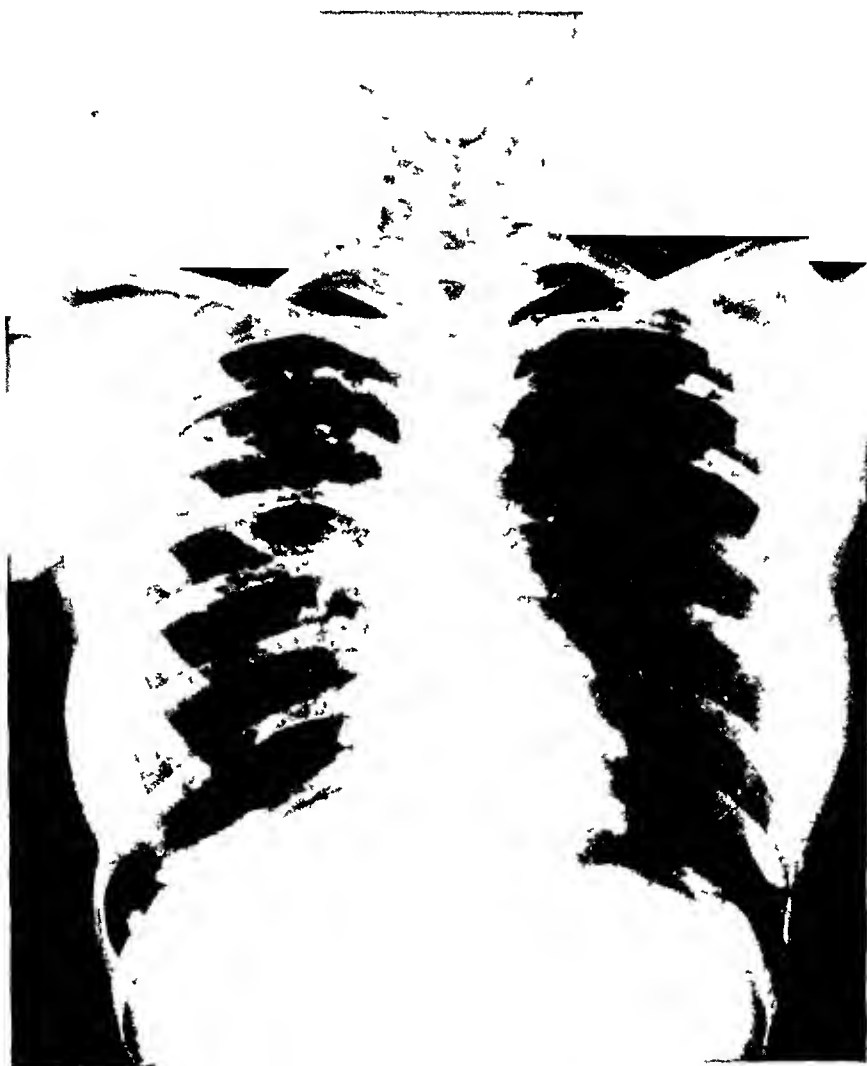


FIG 2 (3-24-36) *Case 1* Absorption of lesion, residual interlobar pleurisy and hilar fibrosis

present symptoms. Examination on admission revealed the patient to be acutely ill with temperature 104° F. Herpes was present on the upper lip and there were signs of consolidation of the right upper lobe. Roentgen-ray (figure 3) confirmed this. The sputum showed pneumococci type III and was negative for tubercle bacilli. The clinical course was characterized by marked toxicity, high pyrexia, and toxic hepatitis. One week after admission the temperature began to decline and gradual improvement of all symptoms was noted. A roentgenogram on March 3 showed complete resolu-

tion of the pneumonia except for a few hilar strands and thickening of the interlobar pleura (figure 4)

Case 3 J L, a 25 year old man, was admitted on December 1, 1934 with a history of chills and fever of two days' duration His temperature was 104° F Herpes labialis was present The general appearance was that of marked toxicity but the most prominent features were nuchal rigidity, hyperirritability, and delirium



FIG 3 (2-17-36) *Case 2* Pneumonic consolidation of right upper lobe, remainder of lungs negative

which were present to such a degree as to suggest the diagnosis of meningitis Spinal puncture was done and examination of the fluid proved negative Physical examination on admission was inconclusive but a roentgenogram on December 3 showed complete consolidation of the left upper lobe (figure 5) Pneumococcus typing of the sputum was unsuccessful, there were no tubercle bacilli present The patient was acutely ill for nine days and then recovered by crisis Roentgen-ray

on December 18 showed resolution of the lesion and a residual thickening of the interlobar pleura in association with a few hilar strands (figure 6)

In the studies of Sante⁶ and Hart⁷ on the postpneumonic lung it was found that pulmonary fibrosis and interlobar pleurisy were among the most frequent complications of lobar pneumonia. These residual effects were



FIG 4 (3-3-36) Case 2 Absorption of lesion, residual interlobar pleurisy and hilar fibrosis

noted in many of our cases. However, there were no follow-up roentgenologic examinations after hospitalization, and it is therefore impossible to state whether or not these shadows subsequently cleared up. In cases of apical pneumonia residual fibrotic lesions are of considerably greater significance than in lower lobe disease because it is more or less customary to in-

interpret all fibrotic infiltrations in the upper lobes as tuberculous without inquiring too carefully into the history of previous pulmonary infection. The clinical and radiologic course of illness in our patients unquestionably established the diagnosis as pneumonia rather than tuberculosis and yet the residual fibrotic infiltrations in no way differed from those seen after resolu-



FIG 5 (12-3-34) *Case 3* Pneumonic consolidation of left upper lobe, remainder of lungs negative

tion of exudative tuberculous lesions. The combination of interlobar pleurisy and pulmonary fibrosis occurred so often after the upper lobe pneumonias as to suggest these sequelae as the ordinary sequence of events. It is therefore obvious that the correct interpretation of these lesions is dependent on the history of the antecedent pulmonary infection.

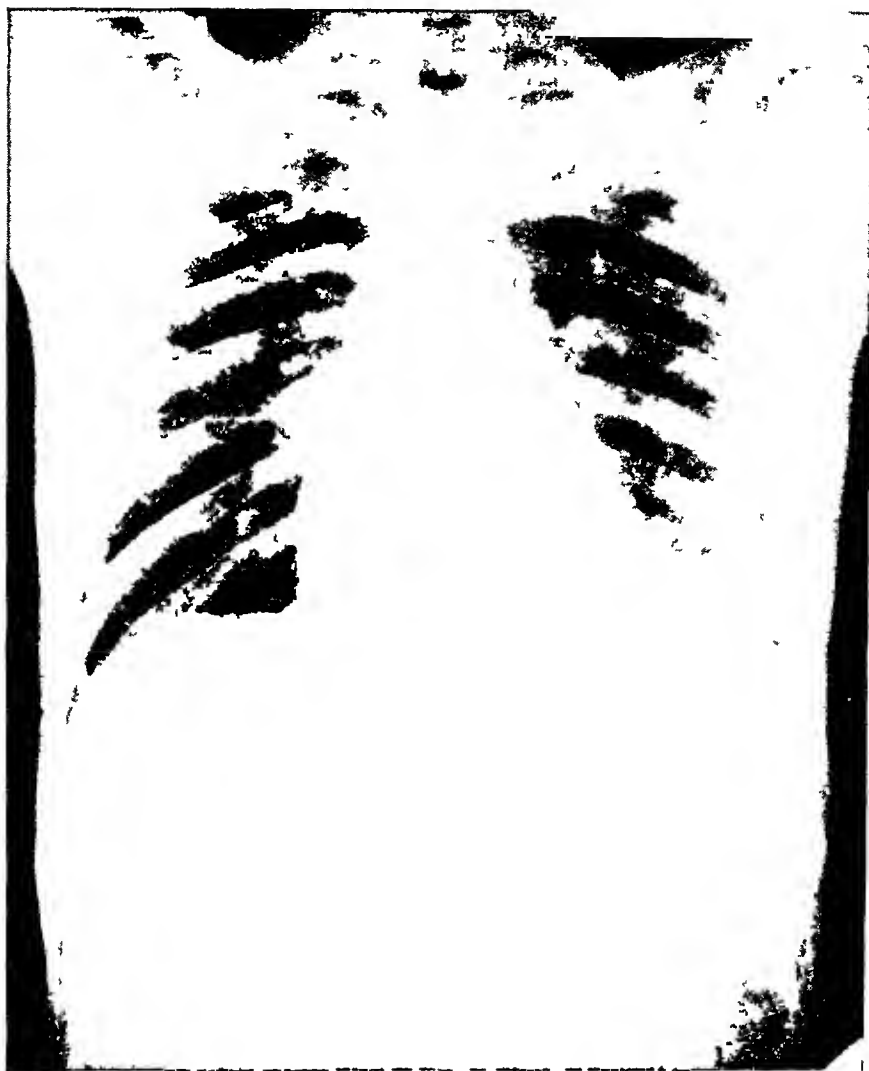


FIG 6 (12-18-34) *Case 3* Absorption of lesion, residual interlobar pleurisy and pulmonary fibrosis extending from hilum (The apparent cardiac enlargement on this film is due to differences in radiographic technic from the previous one)

SUMMARY

1 A statistical study of 180 cases of lobar pneumonia at the City Hospital revealed the presence of upper lobe involvement in twenty-four (13.3 per cent)

2 Involvement of the right upper lobe predominated over that of the left in the ratio of 3:1

3 Examination of the sputum for tubercle bacilli was negative in all instances. Pneumococcus typing was negative for types I-XXXII in half of the cases, in the remainder there was no predominance of any type

4 The course of illness in most instances was characterized by marked toxicity

5 The mortality rate of all the cases was 42 per cent. The mortality rate of the cases with isolated upper lobe pneumonia was 21 per cent and of the cases with multiple lobe involvement 70 per cent.

6 The chief difficulties in the diagnosis are due to the frequent absence of physical signs of consolidation and to the similarity to the lesions of pulmonary tuberculosis. Lung abscess and meningitis may have to be considered also in the differential diagnosis.

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HELIOOTHERAPY OF TUBERCULOSIS¹

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LIGHT therapy, both natural and artificial, is of definite value in the treatment of certain forms of tuberculosis. The clinically effective spectral regions are still to be defined, therapeutically, however, certain advantages are ascribed to sunlight as opposed to artificial sources of light, to one artificial source as against another and even to artificial sources as against the sun.

Empirical evidence still prevails, chiefly because the mode of action of light remains undefined. In the simplest photochemical effects, the physical processes are rarely understood and so the difficulties in biology and therapeutics are understandable. Not even upon the single cell have the effects of light been completely clarified.

Suggestive, however, are the laboratory experiments demonstrating effects upon the reticulo-endothelial system and upon capillary and cellular permeability with their resultant action upon immune processes and upon exchange of colloids and nutrition.

Empirically, however, sunlight represents one of the benefits of outdoor life making for physical and mental well-being. Experimentally in rickets, certain wave lengths of sunshine and artificial sources of light have been shown to be specific. In calcium-deficiency diseases such as rickets and infantile tetany and osteomalacia, ultraviolet energy has proved curative. However, to exaggerate the vital importance of light, either natural or artificial, and to make extravagant claims for it in therapy, employing it to the exclusion of hygienic and dietary regimes, is bound eventually to bring discouragement.

In tuberculosis the nature of the pathologic process must be defined before the indication for light therapy can be stated. Predominantly exudative disease indicates extreme caution, and in pulmonary tuberculosis presents a contraindication.

Benefits from light therapy are undoubtedly obtained by patients suffering from tuberculosis of the bones, articulations, peritoneum, intestine, lymph nodes and larynx when the entire body is exposed to carefully graded doses of natural sunlight or to radiation emitted by certain artificial sources of light rays. The beneficial results of such irradiation are due not only to ultraviolet rays. The visible and infra-red rays, as well as the conditions of the atmosphere, play a certain part in the therapeutic effect.

In superficial tuberculous ulcerations, healing, if it occurs, is due not to direct death of tubercle bacilli caused by ultraviolet energy, but to a local inflammatory or immune reaction of a nature still unexplained. Such ulcers may also heal during general body irradiation when the ulcer itself is un-

* Presented at the St. Louis meeting of the American College of Physicians, April 20, 1937.

exposed Direct irradiation of tuberculous ulcers of the skin, larynx, bronchi and bladder with various sources of ultraviolet has frequently promoted healing, failure may relate to improper dosage, technic or choice of source of radiant energy

In laryngeal tuberculosis, general body irradiation is often effective The acute forms, particularly those with edema, contraindicate local irradiation Vocal silence, bodily rest and electrocautery are much more effective

Oral and pharyngeal tuberculous ulcers, generally secondary, are most resistant to treatment

In tuberculosis of the skin, lupus vulgaris alone can be said to respond specifically to light Scrofuloderma and erythema induratum react favorably at times to general and local exposure, although not as constantly Papulo-necrotic tuberculids are resistant Lupus erythematosus does not respond to and may be aggravated by light

In tuberculosis of the bones and articulations, it is generally agreed that suitable, graded exposure to natural sunlight is most effective in promoting the healing accomplished by orthopedic and other measures Exposure to artificial sources of radiation is valuable as second choice Surgery, solar and artificial light therapy, braces, even in some cases the much maligned plaster-of-paris cast, all have their place in the treatment

It is not to be expected that light therapy will produce new cartilage in place of that which has been utterly destroyed, it does not make the process of fusion less necessary than it has been hitherto, but it can help this develop It is wrong to expect that its use will bring about regeneration of bone equal to that of a few vertebral bodies when they have been destroyed, but when this has occurred and a gibbous deformity exists, light therapy has aided orthopedic treatment in fusing these diseased surfaces especially when employed together with postural treatment

Surgical fusions are less commonly performed on children under 12 years of age If performed on adults or children, the disease must first show some evidence of retrogression, thus surgery is to help nature

Indications for surgical intervention may depend on economic and social conditions, the age of the patient, the joint involved, their number and the stage and extent of the disease, involvement of other organs such as the lungs and kidneys, and complicating abscesses or sinuses Surgical fusion is to be seriously considered in the presence of advanced joint destruction Restoration of function may occur in the synovial form of joint tuberculosis, even in the presence of large effusions, but complete functional return of motion in a joint is doubtful when the bony parts have been destroyed to a marked degree

Following operation, patients are still treated from one to two years, and during this period heliotherapy plays an important part Both mercury arc in quartz, and the carbon arc irradiations, employed as general and local exposures for prolonged periods of time, have proved helpful aids Small joints yield more quickly to conservative treatment than large ones The

knee joint is especially refractory, and particularly obstinate are old fistulas of the spinal column, pelvis or hip

Pulmonary tuberculosis per se is not an indication for light therapy. Uncomplicated exudative pulmonary tuberculosis is a contraindication to light therapy, with proliferative or fibrotic pulmonary tuberculosis, accompanied by elevation of temperature, sunlight or artificial lights, if employed at all, should be used cautiously. Intense sunlight should be avoided, and diffuse daylight or early morning and late afternoon sunlight should be used. Focal or constitutional reactions should be watched for. The indications here resemble those of tuberculin therapy.

In pulmonary tuberculosis, even when quiescent, harm has been done by sunlight exposures, especially with too intense and prolonged irradiations. Solar heat alone, especially in summer, can prove very harmful.

Stationary pleural tuberculosis has often been helped by light therapy. Tuberculous empyemas do not respond.

Genito-urinary tuberculosis deserves a trial of such treatment in combination with other measures. If unilateral renal tuberculosis is diagnosed at the very onset of symptoms and when such symptoms are slight, conservative treatment with light therapy has on rare occasions prevented the need of surgical intervention. As a rule, nephrectomy is indicated.

For unilateral progressive renal tuberculosis or bilateral disease in which the more involved kidney is removed, light therapy is to be advised as a desirable postoperative treatment. It may have a favorable action on the genital organs and the remaining kidney and effectively contribute to the healing of a tuberculous cystitis, whether alone or in association with medical treatment. Light therapy exercises a healing action on the stump of the ureter, which so often shows residual ulceration, resulting in a discharging sinus or a persistent cystitis. It has given excellent results, even with chronic gaping wounds, extensive and deep, and even when covered with ulcerations and tuberculous granulations.

Light is particularly indicated in those not infrequent cases of renal tuberculosis complicated by genital tuberculosis in which the seminal vesicles and prostate are involved, thus often obliging postponement of cystoscopy to avoid trauma of the prostate and the risks of general infection. Therefore, before surgical intervention it is advisable to treat the concomitant lesions with a methodical course of light therapy to make cystoscopy and nephrectomy procedures entailing less risk of dissemination.

In bilateral renal tuberculosis, light therapy is indicated. It may help render the disease quiescent, its occasional analgesic action on ulcerations of the bladder is particularly welcome.

Advanced bilateral renal and bladder tuberculosis has rarely responded to any form of therapy, especially when the patient is cachectic. Postoperative sinuses, especially following nephrectomy, have responded in a large number of cases to light therapy of all forms. Local exposure to ultraviolet rays of circumscribed tuberculous lesions of the urinary bladder has been

shown to yield favorable results, but the method requires special applying devices and, above all, skilful treatment of the bladder lesion

Ocular tuberculosis and aural tuberculosis respond infrequently to light. Corneal ulcers and phlyctenular conjunctivitis not infrequently heal under local exposures

Fistulas are often resistant to such treatment. Postoperative sinuses, in contrast, are most responsive

Intestinal tuberculosis of both the secondary ulcerative and hypertrophic forms especially indicates light therapy and often is rapidly responsive

Artificial light and solar therapy, as well as a rich vitamin diet, should be used in most cases, as they frequently relieve the symptoms and bring about recovery

Excellent results are obtained with the use of artificial sources of radiation, with general exposures either of the mercury arc in quartz, or flaming carbon arc sources. The results depend on factors such as the general status of the patient and the location, extent and nature of the disease in the intestine. Those with far advanced pulmonary and intestinal tuberculosis with little remaining resistance cannot be expected to respond, but intestinal tuberculosis today is healed in many patients, and autopsies have often confirmed this

The loss of symptoms is frequently surprising, abdominal pain and discomfort disappearing, diarrhea and fever subsiding quickly, and general improvement taking place. Roentgenologic studies show that the intestinal irritability as visualized by roentgen-ray defect clears up entirely in many instances

In peritoneal tuberculosis, light therapy always deserves a trial first. The serous exudative type generally responds to light irradiation, both in children and in adults. The dry proliferative form, usually adhesive, is more refractory. When there have been ulcerations and large caseous lymph nodes, as commonly seen in children, the results are most unsatisfactory. When the disease is of long standing, healing is more difficult than when irradiation is begun a short time after onset

The abdominal pain usually disappears rapidly under light therapy, especially in children. Large quantities of ascitic fluid may disappear in a few months

Tuberculous lymph nodes in the stage of hyperplasia generally heal under solar and artificial light therapy. Occasionally they caseate under light treatment and surgical excision may be indicated followed by postoperative light therapy. Caseous nodes respond although less constantly. Liquefied nodes require aspiration followed by light exposures. Sinuses from draining nodes indicate a course of light treatment. General and local irradiation are essential over periods of many months. Not infrequently roentgen-ray exposures may have to be combined. At times incision into a softening node is necessary

In tuberculosis, overdosage has produced harmful focal reactions. Light may set up a focal reaction similar to that of tuberculin.

The erythemic reaction is an accurate indicator of skin tolerance. A preliminary exposure of a small area to gauge the minimal perceptible erythema will generally avoid undue burns.

With any form of tuberculosis, light is to be used as an adjuvant only and should be combined with all other indicated forms of therapy. One of these, namely, roentgen therapy, has many restrictions and important contraindications, especially in pulmonary tuberculosis. Its healing effect in certain forms of extrapulmonary tuberculosis has been definitely established, but the limitations must be recognized, dosage carefully regulated, and treatments given only by experts in the field. The mainstays of treatment are still rest, proper dietary, and hygienic outdoor life.

THE SYNDROME OF EXTRARENAL AZOTEMIA^{*}

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AZOTEMIA signifies an abnormal increase in the non-protein nitrogen (NPN) level of the blood. Normally the blood of a fasting person contains from 25 to 35 mg per cent of non-protein nitrogen, this includes urea, uric acid, ammonia, amino acid, creatine, creatinine and some nitrogenous substances known as undetermined nitrogen or rest nitrogen. Values for blood non-protein nitrogen over 40 mg per 100 c c are considered abnormal.

Theoretically an azotemia could be caused by an increase of any of these non-protein nitrogen constituents. The amounts of uric acid, ammonia, creatine and creatinine are so small that increases of even several hundred per cent would have but little effect on the total non-protein nitrogen. For practical purposes it can be considered that a noticeable increase in the blood non-protein nitrogen is usually due to alterations in the concentration of urea or undetermined nitrogen or both, and very rarely to changes in the amount of the amino acids.

The high non-protein nitrogen values and the clinical picture of uremia produced by bilateral diffuse and usually progressive kidney diseases, such as glomerular nephritis, nephrosclerosis, pyelonephritis, congenital cystic disease of the kidneys, mercuric chloride poisoning, renal tuberculosis, as well as by obstructive lesions in the lower genito-urinary tract due to tumor, stricture or enlarged prostate gland have been adequately described in medical literature.

On the other hand, but little attention has been directed to the fact that high blood non-protein nitrogen values may result from non-renal disease, or be due to functional or to minor pathologic disturbances of the kidneys which are often reversible under proper therapy. Prerenal or extrarenal azotemia are expressions often used to describe such types of azotemia which are not primarily due to renal disease. Unfortunately these terms imply a lack of participation of renal function in the production of the azotemia. Practically all conditions which are designated as prerenal or extrarenal azotemia are accompanied by functional renal changes and occasionally by minor degrees of renal damage. In many cases the term functional renal azotemia could more properly be applied, but because of long usage the term extrarenal azotemia should be retained. The concept of the syndrome should be expanded, however, to include diminished function of the kidney due to local functional, or even to minor pathologic changes. As will be pointed out later, these pathologic changes are often terminal events initiated

^{*} Received for publication August 24, 1937.

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by purely extrarenal factors and cannot logically serve as the basis for the differentiation of a special group. They have been more or less neglected in texts dealing with kidney disease, and for that reason their importance has been overlooked.

Interest in this problem was stimulated by occasional examples of azotemia unrelated to organic kidney disease. A study of the literature in relation to these cases seems to indicate that the azotemia under these circumstances can be explained on the basis of one or more of six fundamental mechanisms. It is the purpose of this paper to present a review of these mechanisms, and to show by means of analyses of our own cases and of those collected from the literature that they will explain azotemia in all conditions not due primarily to organic kidney disease. An analysis of azotemia from this viewpoint allows a much more rational approach to therapy and clarifies an otherwise very confusing aspect of medicine.

BASIC MECHANISMS CAUSING EXTRARENAL AZOTEMIA

1 *Drop in Blood Pressure* It has been adequately established that the hydrostatic pressure in the glomerular capillaries furnishes the potential which induces glomerular filtration¹. The osmotic pressure of the colloids in the blood plasma may be set at about 30 mm of Hg in normal individuals². The glomerular filtration pressure is represented by the difference between the hydrostatic and the osmotic pressure. The hydrostatic pressure, which is directly dependent on the glomerular capillary pressure, is counteracted by the osmotic pressure of the plasma colloids. The effective glomerular filtration pressure is thus produced by the balance in favor of the hydrostatic pressure. Under normal circumstances the urine pressure in the intracapsular space and tubular lumina is too low to affect appreciably the filtration pressure³.

Lassen and Husfeldt⁴ studied the effect of changes in blood pressure on the renal function of normal individuals. A fall in blood pressure was produced by means of spinal anesthesia. It was noted that the urine volume diminished directly with the fall in blood pressure until a systolic level of approximately 70 mm of Hg was reached. As the blood pressure returned to normal, the volume of urine also rose. As a result of their studies, the authors felt that the systolic blood pressure of the peripheral circulation need fall but little below 70 mm of Hg before the production of urine would cease entirely. It is interesting to note that as the volume of urine decreased, the concentration (specific gravity) of the urine increased. It was concluded that with the lowered blood pressure due to spinal anesthesia, the glomerular function of the kidneys varied directly with changes in blood pressure whereas the tubular function remained unchanged as far as the resorption of water was concerned.

The above holds true for persons with normal blood pressure. It is well known that with advancing years the blood pressure rises and it is not

unusual for individuals past the age of 40 to have hypertension of many years duration. Wilkner⁵ raises the question whether or not this habituates the kidneys to depend on a higher filtration pressure, and argues that the threshold at which renal function diminishes in such individuals may be considerably higher than in those with normal blood pressure.

It seems clear, however, that a systemic blood pressure of at least 70 mm of Hg in normal individuals and perhaps higher in those with hypertension is necessary to maintain adequate renal function.

2 Hypochloremia and Hyponatremia In clinical medicine hypochloremia and hyponatremia are encountered in a wide variety of unrelated diseases. Persistent vomiting, gastrointestinal fistulae, diarrhea, excessive perspiration, rhinorrhea, evaporation from destroyed epithelial surfaces and polyuria are among the common causes of salt loss. More rarely, these blood electrolytes may be lost into body cavities (as in ascites) or into interstitial tissues (as in edema or shock). It is evident that in practically all of these cases, fluid loss accompanies the electrolyte loss. In addition, under experimental conditions and probably rarely in clinical practice dietary salt restriction may result in hypochloremia and hyponatremia.

In the past, attention for the most part has been directed to the chloride level resulting from these conditions. It should be emphasized at this point that sodium loss (in varying degrees) is usually associated with chloride loss. The influence of hypochloremia and hyponatremia on kidney function individually and collectively must be considered.

The frequent association of hypochloremia and azotemia has stimulated considerable experimentation and speculation. The many theories evolved and the contradictory experimental data derived have resulted in much confusion.

Blum and his co-workers⁶ believe that urea is retained in the body in order that the osmotic pressure of the body fluids may remain unchanged despite chloride loss. Peters,⁷ as well as Kerpel-Fronius and Butler,⁸ states that non-protein nitrogen may accumulate in the blood because the patients are dehydrated and are, therefore, unable to excrete the proper volume of urine. Peters⁷ and others believe in addition that increased destruction of body proteins may play a part when dehydration is severe.

Certain investigators, Brown et al.,⁹ believe that marked anatomical changes in the kidneys, especially the tubules, may be responsible for the nitrogen retention. Haden and Guffey¹⁰ and Mellinshoff¹¹ ascribe the azotemia to transient renal insufficiency of a purely functional type.

The experiments performed by Haden and Orr¹² in which animals were starved, their duodenum ligated and adequate fluid intake maintained were not conclusive, because Binet and Rathery¹³ repeated this work and showed that dehydration, as indicated by polycythemia, was present when this technique was used. The dogs in these experiments lived an average of four to nine days.

Since these results were not conclusive, Glass¹⁴ performed experiments

in which the chloride loss was definitely separated from dehydration. His dogs were given a carefully measured diet which was salt deficient but adequate in all other respects. The development of hypochloremia was also aided by gastric lavage before meals. By this technic Glass succeeded in producing hypochloremia without dehydration or starvation. The blood sodium level was not determined. The water content of the dog's blood plasma remained normal and the animals lived about 20 days in contrast to the much shorter period in Haden and Orr's experiments. Glass found that when the blood chloride loss reached 30 per cent, the urine and stools contained more nitrogen than could be accounted for by that contained in the food. The blood non-protein nitrogen became elevated slightly during the early part of the experiment and rose to very high levels shortly before death. The terminal stage resembled the clinical syndrome of uremia. Accompanying the terminal azotemia there was a diminution in the urinary excretion of nitrogen. This was interpreted as indicating an early rise of non-protein nitrogen due to an increased protein catabolism and followed by a terminal uremia associated with alteration of kidney function. The terminal rise of non-protein nitrogen and death could be prevented if sodium chloride was given to the animals before coma developed. In view of the fact that blood chlorides had to be reduced 30 per cent before these results followed, it was concluded that mild hypochloremia was less important clinically than pure dehydration.

Landis and his co-workers¹ have recently studied the relation between azotemia and hypochloremia and present an explanation supported by laboratory evidence. These investigators showed that when individuals were kept on a diet of known constant nitrogen intake as well as on adequate fluid intake, the average 24 hour urea clearance varied directly with sodium chloride restriction sufficient to produce hypochloremia. No attention was paid to the blood sodium level. The use of the 24 hour urea clearance technic explains their success as contrasted to the non-conclusive results obtained by other workers employing the standard two hour clearance. The level of the blood urea nitrogen rose with a restriction of the salt intake and the urea clearance diminished. In such individuals, treatment with sodium chloride without changing the nitrogen or fluid intake caused the 24 hour urea clearance to increase and the blood urea nitrogen to drop to normal.

In these cases the authors argued that neither dehydration nor oliguria per se explained the changes in renal function since the fluid intake averaged 4500 c c and the urinary output 3000 c c per day. These experiments were interpreted as indicating that the chloride level of the blood must be considered a factor in renal function entirely distinct from the fluid intake. There is also considerable clinical evidence to support this experimental work indicating that the administration of sodium chloride in selected cases is an aid to renal function^{6, 16}.

McCance¹⁷ produced salt deficiency in four persons with normal kidneys. They were given a plentiful intake of water but caused to perspire profusely

and to take a sodium chloride free diet. Azotemia developed in each case. Renal function was studied in one of these persons. The urea clearance was found to be only 60 per cent of normal. Clausen,¹⁸ on the other hand, could not confirm the findings of Landis or McCance. He was unable to demonstrate any correlation between the blood chloride level and the urea clearance test, or between chloride therapy or restriction and the urea clearance test.

Groak¹⁹ in dogs and Clausen¹⁸ with humans produced azotemia by injection or oral ingestion of large amounts of urea. In no case did the blood chloride level change. They were of the opinion that the chloride level as such did not influence nitrogen elimination.

Kerpel-Fronius²⁰ opened up an entirely new approach to the problem. By means of experiments on rabbits it was shown for the first time that with azotemia due to salt restriction, the important ion was the sodium and not the chloride. Hypochloremia without hyponatremia was produced in one set of animals, in the other the blood sodium was reduced. The animals with hypochloremia, but normal sodium levels, showed no dehydration or azotemia. The group with low blood sodium showed dehydration and azotemia despite an adequate fluid intake.

It remained for Gomori and Podhradzsky²¹ to point out the true significance of the above experiments as applied to azotemia in humans. They believe Kerpel-Fronius' experiments are unimpeachable proof that hypochloremia plays no direct part in the development of azotemia, while sodium restriction by leading to dehydration can cause azotemia.

Basic studies by Gamble²² show that where sodium is lost the body loses the corresponding quantity of water, this loss being from the plasma and interstitial fluids. Gamble's explanation is that the body tries to compensate for the lowered osmosis by a corresponding decrease in water content. In spite of the loss of sodium, the plasma concentration of this ion does not decrease appreciably but the quantity of circulating plasma does decrease. This causes a dehydration similar to direct water reduction. If the blood sodium is low, an increased water intake is of no avail since the newly added fluid does not remain for long in the plasma. Thus, Gomori and Podhradzsky²¹ feel that salt deficiency by producing hyponatremia can cause dehydration even though the fluid intake remains adequate. They attribute the resulting azotemia to the dehydration.

From this recent work it is evident that the cause of the confusion with regard to this subject centers in the fact that many investigators have paid attention to only the chloride portion of the problem. It is also evident that both hypochloremia and hyponatremia influence renal function but by different mechanisms. It is well known, as shown by Gamble,²³ that the loss of electrolyte from the body is always associated with fluid loss, and conversely that fluid loss is associated with loss of electrolytes. What has been overlooked is the fact that the electrolytes are not always lost in the same proportions in various body fluids. For example, the patient who vomits loses fluid, much chloride (as HCl) and but little sodium. This results in a

marked hyponatremia but with relatively normal blood sodium level²³ On the other hand, the loss of pancreatic fluid through a fistula causes a marked hyponatremia with considerably less change in the blood chloride level The proportional loss of sodium and chloride varies with different body secretions and excretions

Chloride loss can probably affect renal function only because of the concomitant loss of fluid which is entailed In this respect, hyponatremia must be considered among the causative mechanisms of extrarenal azotemia Hyponatremia, on the other hand, seems specifically to produce a diminished blood plasma volume irrespective of the fluid intake or loss The azotemia which follows sodium chloride restriction is probably intimately linked with the sodium factor

Aside from the influence on water balance and the level of the nitrogenous products one must not overlook that loss of electrolytes results in a shift of the acid-base balance of the body If sodium is lost in excess of chlorides (i.e. pancreatic juice) acidosis results On the other hand, chloride loss in excess of sodium (i.e. gastric juice) results in alkalosis In this respect, varying degrees of acidosis or alkalosis may accompany the syndrome of extrarenal azotemia

3 *Dehydration* That ordinary dehydration may affect renal function has been well established on the basis of scientific investigations and routine clinical experience Lashmet and Newburgh²⁴ have shown that under normal conditions the kidneys excrete 35 to 40 grams of solids per day Each gram of this waste material requires about 15 c.c. of fluid to be dissolved Therefore even with kidneys working to maximal concentration, at least 500 to 600 c.c. of urine must be excreted per 24 hours to avoid the retention of nitrogenous waste products in the blood If the kidneys are unable to concentrate to the maximal specific gravity of 1.032, more fluid is required to eliminate the total solids This has been carefully worked out by them and is shown in the accompanying table²⁵

Maximum Concentrating Ability		Minimum Amount of Water Required to Excrete 35 grams of Waste Material
Specific Gravity		Cubic Centimeters
Normal	1.032-1.029	473
Diseased	1.028-1.025	595
	1.024-1.020	605
	1.019-1.015	850
	1.014-1.010	1,439

In individuals with normal kidneys, the volume of urine is more or less directly related to the fluid intake This has been adequately and conclusively shown by Coller and Maddock²⁶ who performed experiments planned to demonstrate the effects of pure dehydration on renal function In their experiments all other factors known to affect renal function remained con-

stant throughout. The subjects were healthy adults who were permitted light muscular activity. The environment was such that sweating did not result. A diet of low fluid content, just sufficient to cover the caloric requirements, was given. The mineral content of the diet remained constant throughout with an adequate salt intake so that no disturbance of the mineral balance of the body resulted. These subjects were then dehydrated by merely restricting the fluid intake.

The important changes were found in the blood and urine. The non-protein nitrogen of the blood rose in each case from normal figures of 30 to 32 mg per cent to 40 to 45 mg per cent after two to four days of dehydration. The urines before dehydration showed an average specific gravity of 1.015 with volumes ranging from 1200 to 1500 c c. With dehydration the specific gravities in each case increased to values of from 1.031 to 1.041, while the daily urinary output dropped to 440 to 480 c c. The urine on the last day of dehydration exhibited traces of albumin, many casts and some red cells. This was an interesting demonstration of the lack of specificity of the presence of albumin, casts and red cells in the urine as indicative of organic renal disease.

Following treatment with fluid alone these abnormal findings in both the blood and urine reverted to normal within one or two days. These experiments seem to indicate that pure dehydration entirely aside from salt restriction or loss may have a definite deleterious effect on renal function. In addition to producing oliguria with its concomitant retention of nitrogen in the blood, dehydration may also cause azotemia by other mechanisms. Meyler²⁷ in particular has stressed the point that dehydration increases protein catabolism. This has been borne out by other investigators²⁸. It should not be overlooked that dehydration by reducing the circulating blood volume may produce shock with its accompanying lowering of the blood pressure. These factors are probably effective only in the severer degrees of dehydration.

Except under strict experimental conditions and rare clinical circumstances, dehydration per se does not occur except in conjunction with loss of body electrolytes. Dehydration without salt loss would, therefore, be expected particularly in instances of restricted fluid intake with normal consumption of food. Possibly to be considered with dehydration is shock. Here blood is shunted from the active vascular tree into stagnant body depots such as the liver, spleen, splanchnic area and sub-papillary capillary plexuses. Aside from the drop in blood pressure, renal function is impaired under such circumstances by the lack of available fluid in the active circulation. The blood passing through the kidneys is dehydrated even though no fluid is lost from the body as a whole.²⁹

With dehydration there occurs hemoconcentration which entails an increase in viscosity of the blood.³⁰ This probably hinders the circulation through the kidney. Medes³¹ has shown that decreased blood flow through the kidneys leads to a diminution of the glomerular filtrate. Dehydration

also increases the concentration of total blood protein³² The influence of this fact on renal function will be discussed later

In summary then, dehydration affects renal function by limiting the available fluid for excretory purposes, increasing protein catabolism, diminishing the flow of blood through the kidneys, lowering of the blood pressure, and probably by increasing the colloid osmotic pressure of the blood

4 *Liver Damage* Although many of the metabolic functions of the liver were known earlier, it was not until the work of Mann and his co-workers³³ that certain of these functions were definitely established Of particular interest in relation to the subject under discussion is the experimental proof presented establishing the liver as the site of catabolism of amino acids with the consequent production of urea Bollman, Mann and Magath³⁴ in studies on hepatectomized dogs, found that in no case did deaminization occur after the liver had been removed This was demonstrated by the recovery of amino acid in the blood, urine and tissues of these animals in amounts approximately equal to the anticipated formation of urea If amino acids were injected into these animals the entire amount of amino acid nitrogen was recovered unchanged in the blood, thus little or no urea is formed in the absence of liver function In these experimental animals, although the total non-protein nitrogen increased, this increase was associated with an absolute reduction of urea nitrogen and a marked rise in the amino acid nitrogen of the blood

Clinically this has a definite bearing in cases of advanced liver destruction Prior to the experimental work of Mann and his co-workers, Stadie and Van Slyke³⁵ reported a case of acute yellow atrophy which demonstrated these findings Even more striking, however, is the case of extreme liver destruction reported by Rabinowitch³⁶ in which the amino acid nitrogen rose to 216 mg per cent (as contrasted with normal value of from 5 to 8 mg per cent) No urea could be demonstrated in this instance From a similar point of view, Stander³⁷ in reporting a chemical study of chloroform poisoning, found an increase in the total blood non-protein nitrogen with which was associated an increase in the amino acid nitrogen More recently the studies of Wakeman and Morrell³⁸ on experimental yellow fever in monkeys demonstrated that in this disease, which is characterized by liver cell damage, the blood urea nitrogen, although increased in most instances, did not increase in proportion to the total non-protein nitrogen In some cases it showed an actual decrease The difference in every case was made up chiefly by a rise in the amino acid nitrogen and undetermined nitrogen

In the past few years there have been many case reports of azotemia subsequent to varying degrees of liver damage in which the rise in total non-protein nitrogen was due to a rise in the urea nitrogen rather than the amino acid nitrogen Few of these cases, however, have received adequate study from the point of view of various other factors such as hypochloremia, hyponatremia, drop in blood pressure, dehydration and renal function

This recognized deaminizing function of the liver demonstrates the im-

portance of both amino acid and blood urea nitrogen determination in persons with liver disease. Obviously in the absence of such determinations no true understanding of elevated non-protein nitrogen in liver disease can be obtained.

5 *Protein Catabolism* Under ordinary circumstances the level of the non-protein nitrogen of the blood is dependent on (1) the adequacy of renal function in eliminating nitrogen in the urine, (2) on the amount of water available to perform this function and (3) on the rate at which protein is broken down in the body³⁹. With proper function and available fluid present, an increased rate of protein catabolism is reflected up to a certain point by an increase in urinary excretion of nitrogen. It seems reasonable to assume then that protein catabolism may occur at so rapid a rate that even normal kidneys are ineffectual in removing all of the nitrogen products produced, or too rapidly for normal kidneys to be adjusted immediately to this increased demand. In either case an increase in the level of the blood non-protein nitrogen will result.

The importance of protein catabolism in controlling the level of the non-protein nitrogen of the blood has been emphasized by Peters and Van Slyke⁴⁰. They have pointed out that unless the rate of nitrogen catabolism and the urine volume are known, the blood non-protein nitrogen cannot be utilized as a criterion of renal function. Conversely, it would seem that in the presence of normal renal function and urine volume, an increase in the blood non-protein nitrogen can be associated with increased protein catabolism.

In controlled starvation experiments Lennox et al⁴¹ demonstrated fluctuations in the blood non-protein nitrogen presumably due to uneven protein catabolism. A previous investigation in animals had been made. Morgulis and Edwards⁴² reported an increase of the non-protein nitrogen and blood urea nitrogen at an early stage of fasting which remained at a more or less fixed level until the extreme stage was reached when a much greater increase occurred. The amino acid nitrogen and creatinine remained more or less constant but the undetermined nitrogen rose somewhat. The investigations of both of the above groups indicate that on re-feeding, for a time less nitrogen is excreted than ingested. It would seem likely, therefore, that the non-protein nitrogen which leaves the blood in these instances is not excreted but used in building body protein.

Morgulis and Edwards⁴² and Mackay and Mackay²⁸ have shown that when water as well as food is restricted, the rise in the non-protein nitrogen is exaggerated. The latter investigators reported the additional increase of non-protein nitrogen in dehydration experiments further prolonged by intravenous injections of sucrose. Peters and Van Slyke⁴³ point to this rise of non-protein nitrogen as the result of augmentation of protein metabolism and consider it as an example of toxic destruction of protein. Meyler²⁷ has presented evidence to indicate that dehydration may be an important factor in increasing protein catabolism. It is also considered by some²⁷ that

acidosis may play a similar rôle Glass,¹⁴ in the experiments previously mentioned, was able to show that chloride (Cl^- salt) loss leads definitely to some degree of protein destruction

In a series of experiments on the effects of protein intoxications and injury of body protein Cooke and Whipple⁴⁴ and their collaborators⁴⁵ point out the occurrence of high non-protein nitrogen with sterile abscess formation, septic inflammations such as pleurisy, pneumonia and peritonitis in experimental animals, and in man with septicemia, peritonitis and pneumonia. In these works the azotemia was accepted as an indication of increased protein catabolism in the presence of anatomically normal kidneys

Recently Lurje⁴⁶ in continuing the investigations on protein metabolism in instances of severe surgical trauma in cases with intact innervation of the liver has demonstrated an increase in the amino acid nitrogen of the blood which appears to be due to a reflex provoking endogenic breaking down of proteins

Cases reported by Rackemann, Longcope and Peters⁴⁷ of nitrogen retention occurring in the course of acute allergic states are very interesting in view of the interpretation that these are due to some degree of tissue injury. Also, Hashimoto⁴⁸ has shown that with histamine intoxication similar changes in the blood chemistry take place. Although protein metabolism is believed to be partly responsible for this change, it must not be forgotten that at autopsy Hashimoto⁴⁸ found marked degenerative changes of the tubular epithelium

In extensive studies of nitrogen metabolism as affected by iodides Grabfield and Prentiss^{49, 50} determined that iodides caused an increased nitrogen excretion probably resulting from increased nitrogen catabolism. In the case of potassium iodide, however, the deleterious effects of potassium on kidney function must be remembered

To recapitulate, there seems to be evidence to indicate that the factors of starvation, dehydration, acidosis, salt loss, infections, fever, trauma, allergy, and certain drug intoxications may all be associated with increased protein catabolism. There is some doubt, however, as to whether these factors operating independently can produce a significant degree of azotemia. It is perhaps better to consider them as contributory factors, since under actual clinical circumstances, they are usually interrelated with other mechanisms capable of producing azotemia

6 Local Renal Disturbance That progressive organic kidney disease may alter renal function is so well known that it requires no further comment. On the other hand that minor changes in renal tissue may cause alterations in function which are often reversible is not so well appreciated. These may occur in a wide variety of unrelated systemic diseases, and are characterized by diversified change in the kidney parenchyma and resultant alterations in renal function. Only too often are these minor changes noted at autopsy with no attention paid to them in explaining physiological dis-

turbances Likewise, it is often overlooked that disturbances in the kidney of a functional nature can result in diminution of excretion of urine

The factors which influence the output of the urine will be briefly reviewed in order that the concept under consideration may be more clearly understood Cubitt,³ in a recent review on renal physiology summarizes them as follows (1) The urine pressure, (2) Changes in the secretion-reabsorption activity of the tubule cells, (3) The blood pressure in the glomerular capillaries, (4) The area of the capillary bed from which filtration is taking place, (5) The osmotic pressure of the colloids in the plasma of the blood contained in the glomerular capillaries, (6) Nervous control and (7) Hormonal control

Whether changes in the secretion—reabsorption activity of the tubule cells can account for changes in renal function is still problematical It is possible that the activity of the tubule cells may be changed by alteration in blood supply, pressure of urine within the tubules, and microscopic changes within the tubule cells For a similar reason the control of the area of the capillary bed from which filtration can take place must be disregarded It can not be measured readily in the living, nor can it be seen in anatomical material It is evident that the control of this area must depend on systemic blood pressure, nervous influences presence or absence of chemical substances or hormones present in the blood, and on the state of relaxation and contraction of the afferent and efferent arterioles controlling the blood supply to the glomeruli Since the kidney normally needs but a small fraction of its total glomeruli for normal renal activity, it seems unlikely that anything except a diffuse change would result in loss of renal function severe enough to cause nitrogen retention Because the afferent and efferent arterioles are under nervous and chemical control it is conceivable that a widespread loss of effective filtering area could result through some humoral stimulation or nervous reflex

The principal function of the renal nervous control is regulation of the vasomotor functions with vaso-constrictor action predominating Any stimulation of the splanchnic trunk (either directly or perhaps indirectly from a distance by reflex action) lessens the amount of urine secreted Conversely, depression or section of the splanchnics increases the amount of urine⁵¹ There is no good evidence that nerves carry secretory fibers⁵¹ The nature of reflex anuria is obscure and will be discussed in detail later

The effect of the systemic blood pressure on urinary function has already been mentioned It was pointed out that the effective filtration pressure depends on the difference between the hydrostatic pressure of the blood due to the general arterial blood pressure, and the counter pressure due to the osmotic tension of the serum proteins This holds true as long as the urine pressure on the tubular side of the glomerular membrane is not increased Normally the intracapsular urinary pressure is nil and can be disregarded Any rise of the urine pressure in the intracapsular and tubular spaces, however, interferes with the effective filtration pressure Such in-

creases in urine pressure can result from partial or complete obstruction of the kidney tubules

Under normal circumstances the colloid osmotic pressure of the blood rarely exceeds 25 to 30 mm of Hg². This pressure depends chiefly upon the blood proteins. It is well known that in severe states of dehydration hyperproteinemia results³². Gorom and Podhradszky²¹ measured the colloid osmotic pressure in animals before and after dehydration. The average normal for cats before dehydration was 33 mm of Hg. Even though the albumin-globulin ratio reversed with dehydration, the osmotic pressure of the blood proteins increased, reaching in some cases over 60 mm of Hg. They considered the hyperproteinemia due to dehydration an important factor operating within the kidney in the extrarenal azotemic syndrome. This effect is obtained by counteracting the glomerular filtration pressure.

Changes in the renal tubules are not specific and may occur in the course of a wide variety of clinical conditions. Not only are the clinical pictures with which they are associated variable, but often the changes themselves vary from microscopic degeneration to evidence of gross necrosis and, on occasion, are entirely absent. In addition, obstruction can occur from precipitation of material present in the glomerular filtrate, thus occluding the tubular lumina⁵². It would appear that these changes are not necessarily progressive in nature, and, as a rule, disappear as the patient recovers from the systemic condition with which they are associated. They are noted at autopsy only when a patient dies during the course of disease prone to produce tubular damage. At this time changes varying from cloudy swelling to actual necrosis of tubular epithelium with inspissation of granular debris in the lumina of the tubules may be noted.

Experimentally it has been shown that advanced as these changes may be, if given the opportunity, regeneration and presumably return of normal function will take place⁵³. These tubular changes (even though anatomical) must be considered as appertaining to the mechanisms of this syndrome, since they are often produced by the prolonged presence of factors of purely extrarenal origin. The widespread presence of such changes can cause the kidney volume to be increased and the capsule of the kidney to be distended. At autopsy, such kidneys are increased in weight and are grossly edematous and swollen, with bulging of the cortex when the capsule is cut.

These changes in the anatomical structures of the tubular cells invariably result either in an increase in the size of the cells or in the extrusion of cellular debris into the tubular lumina. The end result in either case is a diminution of tubular patency which in turn increases the urine pressure within the tubular and intracapsular space. If the increase in urine pressure is sufficient it may counteract effective filtration through the glomerular capsule and lead to retention of nitrogenous waste products in the blood³.

The cause of tubular changes is not clear. One possible explanation is illustrated by the interesting series of animal experiments performed by

Hashimoto⁴⁸ He showed that after the intravenous injection of 1 to 3 mg of histamine dichloride evidence of intoxication could be expected. This toxicity was associated with a rise of the blood non-protein nitrogen, fall of blood pressure, and markedly diminished urinary flow. The post-mortem findings were definite and characteristic, consisting of diffuse degenerative changes in the tubular epithelium with no changes in the glomeruli. One cannot fail to recognize the resemblance between this picture of histamine shock as described by Hashimoto, and that of extrarenal azotemia as depicted in this paper. In view of the possibility that histamine, or a histamine-like substance, may be liberated in many shock-like states, it seems more than justifiable to include histamine as one of the possible factors in the production of extrarenal azotemia.

Aside from these anatomical changes in the tubular epithelium another mechanism may lead to an increase in urine pressure with a consequent diminution in renal function. It should not be overlooked that the systemic venous pressure when increased may lead to congestion and edema of the kidney. The capsule of the kidney prevents renal distention beyond a certain volume. Therefore, as venous pressure rises, the intrarenal pressure is also increased and is transmitted equally in all directions. At a certain point this will necessarily result in compression of the tubules and thereby raise the urine pressure within the intracapsular space. This in turn diminishes the effective filtration pressure and may lead to oliguria and azotemia. In addition to its effect in increasing the urine pressure, venous congestion influences urinary function by diminishing the blood flow through the kidney and by producing an anoxemia.⁵⁴

One cannot overlook the possibility that renal function may be partially influenced by hormonal control. Of the various endocrine glands in the human body, there is evidence that specific hormones from the pituitary gland and the adrenals exert such an influence.

The diuresis inhibiting action of posterior pituitary lobe extract in man has been recognized for many years. Starling and Verney produced this effect on an isolated kidney and it has further been shown that the effect is not altered by denervation of the kidney. This indicates that the anti-diuretic effect of posterior lobe extract is primarily on the kidneys. Although the exact site of action in the kidneys is still undecided upon, the bulk of the evidence seems to indicate that the antidiuretic action of this hormone is due to increased reabsorption of water without much change in the rate of glomerular filtration.⁵⁵ The indiscriminate use of pituitrin, especially in postoperative cases where the fluid balance is readily disturbed, may well be a significant factor in producing azotemia.

Loeb et al.⁵⁶ have demonstrated that adrenal cortical substance influences sodium excretion. This has been well substantiated by others. In considering the azotemia found in Addison's disease, Loeb and his co-workers⁵⁶ were unable to explain it by purely extrarenal factors. From the evidence on hand, they postulated "that the adrenal cortical substance acts on the

kidney to control the excretion not only of sodium but also of urea. In adrenal insufficiency, the rate of salt excretion is increased while urea elimination is retarded." This hypothesis is attractive in view of the adenal damage commonly found in severe infections and certain toxic conditions (i.e. burns) in which azotemia is not uncommon.⁵⁷ It is evident that a disturbance in adrenal physiology may at times play a rôle in the initiation of extrarenal azotemia.

Discussion It should be kept in mind that these six mechanisms, although presented separately, are interlinked and often interdependent. This method of presentation serves merely to clarify an otherwise extremely complex exposition. The interrelationship of these mechanisms is well exemplified by a hypothetical situation. In a patient who has a severe diarrhea, there is an entailed loss of fluid, sodium and chloride with resulting dehydration and diminution of the circulating blood volume. There is then an associated fall of blood pressure. Starvation, dehydration, fever and hypochloremia would increase protein catabolism. If the patient is severely toxic, renal tubular damage may supervene. This combination of circumstances brings on the extrarenal azotemic syndrome. One can imagine many situations in which the combinations of mechanisms would be much simpler and others where they would be more complex.

The concept of extrarenal azotemia cannot be rationally expounded without considering factors operating locally in the kidney. Renal tubular damage or tubular occlusion may be found terminally in many cases with azotemia primarily due to extrarenal factors. It is not, however, an invariable finding. For this reason such cases can more rationally be placed in the extrarenal syndrome than segregated in some unsatisfactory subgroup of organic renal disease.

The very term "extrarenal" is a poor one, but serves as a useful designation to separate this type of azotemia from that due to the well recognized organic renal diseases. All the extrarenal factors (no matter how far distant from the kidney may be their source) produce, either directly or indirectly, some effect which operates directly in the kidney.

PATHOGENESIS OF EXTRARENAL AZOTEMIA IN VARIOUS CLINICAL CONDITIONS

Azotemia occurs frequently in clinical conditions other than those associated with organic kidney disease. This type of azotemia is extrarenal in origin. While it is more commonly seen in certain clinical states, it may be present in any disease in which the above mentioned mechanisms are operative. An attempt is made here to indicate the pathogenesis of extrarenal azotemia by analyzing the responsible mechanisms in a series of chosen clinical conditions which are illustrated in part with our own case histories. A similar approach is possible under any circumstance in which azotemia occurs in the absence of organic kidney disease.

1 Coronary Thrombosis

Case 1 A 63 years old man was admitted to the Evans Memorial Hospital with a two day history of precordial distress, faintness, vomiting, restlessness and dizziness. Significant physical findings included cyanosis, slight dyspnea, a few râles at the bases of the lungs, distant heart sounds of tic-tac quality, and a pulse rate of 140. Blood pressure was 90 mm of Hg systolic and 70 mm of Hg diastolic. Temperature was 100° F.

The first urine specimen had a sp gr of 1.025, a slight trace of albumin, no sugar, and a few leukocytes and casts per high power field in the sediment. Subsequent specimens of urine were of even higher specific gravity. The leukocyte count was 20,000 with 85 per cent polymorphonuclear neutrophils. The electrocardiographic findings were typical of an acute coronary occlusion. The patient rapidly grew worse and died two days after entry. The blood pressure and pulse were unobtainable for 24 hours before death.

The pertinent laboratory data are summarized in table 1.

TABLE I

Date	B P	Blood N P N mg %	Blood Urea N	CO ₂ Combining Power	Whole Blood Chlorides	Sp Gr of Urine
1/6/37	90/70	45	20	57	433	1.025
1/7/37	?	71	38	49	370	1.030

The autopsy revealed the presence of considerable sclerosis of the coronary vessels with massive infarction of the left ventricle. Grossly the kidneys were normal. Microscopically the glomeruli were normal, but the tubular cells were swollen, often acidophilic, with some of the lumina containing granular debris.

The occurrence of azotemia in coronary thrombosis is not often mentioned but Steinberg⁵⁸ found the non-protein nitrogen of the blood to be over 40 mg per cent in 20 of 31 cases. An analysis of the mechanism of the disease readily explains this frequency of azotemia. A drop in blood pressure, even to shock levels, is common. The effect of this on renal function has already been discussed. The other major factor contributing to azotemia is the diminution in the volume of circulating blood. This may be due in part to vomiting, sweating or to fluid restrictions. The chief cause, however, as shown by Fishberg et al⁵⁹ is the redistribution of the blood, whereby a smaller fraction of the total volume of blood in the body remains in active circulation, and a larger fraction stagnates in dilated capillaries and perhaps within the blood depots. In other words, the features of the shock syndrome are prominent. This, by limiting the fluid available for renal excretion, further influences the retention of nitrogenous waste products.

The urinary findings have been strikingly presented by Steinberg⁵⁸. Most urines showed high concentrations, specific gravities of 1.020 or higher, with the presence of albumin, casts and occasionally red blood cells. In a few instances urinary suppression was complete. Oligurias with 24 hour volumes of 500 c c or less were common.

Starvation, destruction of body protein, toxic damage to renal tubular cells and venous congestion due to heart failure may at times play lesser rôles in producing the azotemia

As shown by Steinberg,⁵⁸ and by analysis of the above factors, it is obvious that a blood non-protein nitrogen which remains elevated or continues to rise is of ill omen and offers a poor prognosis. Serial blood non-protein nitrogen studies and urine analyses should be included along with the electrocardiogram, white blood count and sedimentation rate in evaluating cases of coronary thrombosis.

Case 1 is a classical example of azotemia due to coronary thrombosis. Postmortem examination showed that the kidneys were essentially normal for this person's age, except for the recent tubular changes. Vomiting, drop in blood pressure and the shock syndrome were the responsible factors. The urine with its high specific gravity of 1.025 to 1.030 and the presence of albumin, cells and casts was characteristic. There was in addition a mild hypochloremia. Tubular damage was probably minimal.

2 Alkalosis

Case 2 A 31 year old man was admitted to the Boston City Hospital with a history of a duodenal ulcer of several years' duration. A dietary regime and alkaline powders had afforded relief until about eight months previously when symptoms recurred. The patient then resorted to daily self-induced vomiting. He became nervous and irritable, and developed vertigo, nocturia and shooting pains and aches in both legs.

Physical examination showed epigastric tenderness, tenderness of the leg muscles and active reflexes. His blood pressure was 120 systolic and 90 diastolic.

The history, examination, laboratory data and course are typical of alkalosis.

The significant laboratory data are given in table 2.

TABLE II

	N P N mg %	Plasma Chlorides mg %	CO ₂ Comb Power Vol %	P S P %	Urine Sp Gr	B P	
						Systolic	Diastolic
4/13	130	430	82	6	1.010	120	90
4/14	120	485	65		1.014	120	80
4/15		500					
4/20			60	10			
4/22	98	508	45				
4/29	82	520	40		1.011	120	80
5/30	63	585	42	20	1.012		
6/24	50	588	42	28	1.010	120	80

The patient was given four liters of fluid daily with 30 grams of sodium chloride. Alkalies were omitted. The vomiting ceased after one week, and the nocturia disappeared after the first month.

The syndrome of alkalosis is characterized chemically by azotemia, hypochloremia, and increased carbon dioxide combining power. It may oc-

casionaly occur solely from excessive loss of hydrochloric acid (vomiting of gastric juice) The blood sodium level may be normal Ingestion of alkali by persons with organic renal disease readily causes alkalosis In addition ingested alkaline salts may cause alkalosis if the fluid and chloride balance of the body are disturbed by vomiting, hematemesis, or excessive sweating This phase of the subject is discussed at length elsewhere by Jeghers and Lerner⁶⁰ In addition, it has been shown that severe alkalosis can cause damage to the tubules of the kidney, thus further diminishing renal function⁹ When tubular damage occurs, loss of ability to concentrate the urine may follow The process seems to be reversible if treatment is prompt

It is uncertain whether the ingestion of alkalis can cause renal impairment in a person with normal kidneys unless some auxiliary mechanism be present A case reported by Steele⁶¹ suggests that it can A man, aged 52, had ingested alkalis for years There was no evidence of renal disease prior to this therapy Renal failure developed without clinical symptoms of alkalosis The blood urea nitrogen rose, phenolsulphonaphthalein excretion and urea clearance were diminished, urinary concentration was fixed at a sp gr of 1.010 and albumin casts and red cells were present in the urine Withdrawal of alkalis caused a prompt drop in blood urea nitrogen It was not until three years later that urinary function was entirely normal

Case 2 is an interesting example of alkalosis An admission to the hospital four years before had shown normal renal function The ingestion of alkaline powders, in the presence of diminished chloride and fluid due to vomiting initiated the syndrome Renal tubular damage resulted Even when the blood chemical findings had returned to normal, the phenolsulphonaphthalein excretion was still low and the urine specific gravity fixed at a low level This patient was seen one year after discharge, at this time he had regained normal renal function, including ability to concentrate

3 *Pyloric Obstruction*

Case 3 A 61 year old man was admitted to the Boston City Hospital, complaining of anorexia, pain in the left flank, small nodules in the skin and loss of weight

Scattered pea-sized, non-tender nodules were made out in the subcutaneous tissue of the face, neck and back A walnut-sized nodule was palpable in the left supraclavicular fossa The blood pressure was 175 systolic and 100 diastolic A vague sense of resistance was made out just above the umbilicus

The kidneys showed an ability to concentrate to a maximum of 1.033 On occasions a slight trace of albumin was noted, otherwise the urines were negative The non-protein nitrogen was 35 mg per cent on admission, but two days later the patient developed intractable vomiting and the non-protein nitrogen rose to 125 mg per cent The plasma chlorides fell from 570 to 426 mg per cent Death occurred one week after admission The blood pressure remained well sustained

The autopsy revealed extensive carcinomatosis with metastases to the vertebrae, pelvis and skin The primary lesion was an obstructive pyloric carcinoma The

combined weight of the kidneys was 270 grams and they were grossly and microscopically within normal limits

That azotemia may complicate pyloric obstruction has been well shown, both experimentally and clinically⁹ The above case is a good example of azotemia due to this cause The mechanism is easy to understand Vomiting causes loss of fluid and of chloride The effect of this on renal function has already been discussed In this particular case, the renal tubules were normal at autopsy Occasionally if the syndrome is prolonged, tubular damage may result with concomitant loss of power to concentrate the urine With the tubules normal, as was the case here, the urine is highly concentrated and scanty

4 *Peritonitis*

Case 4 A 59 year old woman was admitted with a known history of a peptic ulcer of ten years' duration Three days before she had developed sudden epigastric pain, abdominal distention and vomiting The vomitus became blood-streaked, probably from retching

On entry the patient was semi-stuporous, the skin was dry, râles were heard at both bases, and the blood pressure was 60 systolic and 10 diastolic The abdomen was distended and tender, most markedly so in the right lower quadrant Definite tenderness was noted on rectal examination The temperature was 97° F, the pulse 120, and the respirations 30

After admission the temperature rose to 102°, and she lapsed into coma The urinary output was only 40 c c in 24 hours despite the fact that fluids were forced The patient died four days after admission

The specific gravity of the urine was 1.019, a very slight trace of albumin was noted and a moderate number of leukocytes and rare granular casts was seen in the sediment The non-protein nitrogen on admission was 55 mg per cent and rose to 100 mg before death

The autopsy confirmed the clinical impression of peritonitis resulting from a ruptured duodenal ulcer The combined weight of the kidneys was 240 grams Microscopic examination revealed the presence of a minimal degree of nephrosclerosis and considerable swelling of the tubular epithelium which in some places was desquamated

In peritonitis we have many mechanisms operating to produce an azotemia Dehydration is caused by vomiting and shift of available circulating blood volume Salt loss will usually accompany this fluid loss Blood pressure is often low Fever, infection, and starvation increase protein catabolism In addition, it is not unknown for the tubular epithelium of the kidney to show changes varying from swelling to actual necrosis with plugging of the tubular lumina This adds a local renal factor to those of extra-renal origin Case 4 shows how all these factors can be operative in a single patient

5 *Liver-Kidney Syndrome* There has been considerable discussion in the recent literature concerning the so-called liver-kidney syndrome^{62, 63} Chief interest has been centered in the attempt to find the noxious agent which is supposedly elaborated by a damaged liver and which secondarily

affects renal function⁶⁴ It is obvious that the azotemia in many of the cases of this syndrome which have been reported, can be explained on the basis of the mechanisms discussed in this paper A recent paper by Lichtman and Solval⁶⁵ emphasizes this point of view The following two cases illustrate this point

Case 5 A 35 year old woman was admitted to the Boston City Hospital, with a history of eructations and of vomiting once or twice weekly for six months Jaundice and weakness had been noted for two weeks, and the patient had become delirious 24 hours before her admission

Physical examination showed a markedly icteric skin with scattered petechial hemorrhages The tongue was dry The liver edge was not felt but the spleen was palpable 1 cm below the costal margin Respirations were 12, pulse 104 and the temperature 102° F Blood pressure was 70 mm Hg systolic and 50 mm diastolic

The specific gravity of the urine was 1.032, there was a slight trace of albumin The sediment was loaded with granular and hyaline casts The patient could not be roused from her coma and died 12 hours after admission The blood non-protein nitrogen was 250 mg per cent

The autopsy revealed petechial hemorrhages in all the serous surfaces The liver was very small, weighed 680 grams, and showed the characteristics of acute yellow atrophy The combined weight of the kidneys was 260 grams Bile staining, and degeneration of the tubular epithelium, and hemorrhages about the tubules of the cortex and medulla were noted microscopically

It is unfortunate that complete chemical studies were not available in this case, but in view of the very high non-protein nitrogen and the extremely small liver, certain deductions are warranted The azotemia here may well have been mostly amino-acid nitrogen retention due to massive liver destruction This case closely resembled the one reported by Rabino witch³⁸ which showed a liver weighing 650 grams, dehydration and fall in blood pressure

Case 6 A 67 year old man was admitted to the hospital because of the development of nausea and vomiting one and one-half weeks after an injection of neoarsphenamine It had also been noted that the skin had become yellow and the urine dark in color

On physical examination a moderate degree of jaundice was observed The abdomen was tympanitic and distended and the liver edge was made out 8 cm below the costal margin The temperature was 98° F, the pulse 100 and the respirations 18

The maximum specific gravity of the urine was 1.027 A very slight trace of albumin was present and an occasional granular cast was noted in the sediment

The patient gradually became worse, and the liver edge seemed to recede about 1 cm daily At the end of a week he developed generalized edema, sank into a quiet coma and died The pertinent laboratory findings are given in table 3

The autopsy showed an extensive hepatitis presumably due to arsphenamine The combined weight of the kidneys was 360 gm Microscopically they showed bile staining and a moderate degree of degenerative change in the tubular epithelium

In this case the azotemia was due to retention of urea nitrogen The amino acids remained normal Dehydration was minimal The single chloride determination gave a high normal value The low level reached

TABLE III

Date	N P N mg %	Blood Urea N mg %	Amino Acid mg %	Uric Acid mg %	Plas- ma- Chlo- rides mg %	T P gm %	Alb Glob		B P mm of Hg	
							gm	%	Systolic	Diastolic
11/9	30								115	70
11/18	74	34		2 5	671	6 8	2 9	3 9	70	50
11/20	60	44 9	7 2			7 0			40	20

by the blood pressure was striking Autopsy showed evidence of mild damage to the tubular epithelium of the kidneys

6 *Yellow Fever* In a series of careful studies on the chemistry and metabolism in experimental yellow fever Wakeman and Morrell³⁸ pointed out that, although the blood urea nitrogen increased in most instances, it did not increase in proportion to the rise in the total non-protein nitrogen In some instances the urea fraction was actually decreased, a proportionate increase occurring in the amino acid nitrogen and also in the "rest nitrogen" The terminal increase in the non-protein nitrogen was further accentuated in most cases as a result of late shock In such instances the blood pressure dropped markedly and oliguria or anuria developed A part of the terminal increase in the azotemia may also be due to the high rate of protein destruction characteristic of the disease The ability of the kidneys to produce urine of normal concentration seems to be almost unimpaired throughout the disease

7 *Gastrointestinal Hemorrhage*

Case 7 A 50 year old man was perfectly well until 10 hours before admission to the hospital when he had sudden nausea and began vomiting blood About a quart of blood was vomited by the time he was admitted to the hospital A history of chronic alcoholism was obtained

On admission the patient was obviously in shock, the pulse was weak and thready and the respirations were 26 per minute The blood pressure was 95 systolic and 55 diastolic The remainder of the physical examination was not remarkable

The patient was given morphine and intravenous fluids He continued to vomit blood On the second day he was given a transfusion of 500 c c and saline clyses, and seemed somewhat improved On the fourth day, however, he began vomiting again, the temperature rose to 100° F and he died

The pertinent laboratory findings are given in table 4 The urines showed a specific gravity of 1 014 and were otherwise negative

TABLE IV

Date	Hgb per cent	R B C in millions	W B C	N P N mg per cent
7/29/34	70	4 2		
7/30/34	69	3 2	21,800	81
8/2/34	50	2 4		218

The effects of blood loss on the level of the blood non-protein nitrogen were clearly indicated by Taylor and Lewis⁶⁶ and later by Buell⁶⁷ More recently, particularly in Denmark,⁶⁸ this problem has received considerable careful attention It seems clear that at times massive gastrointestinal hemorrhage can cause a marked azotemia

Here, as in other conditions, several factors come into play which may affect renal function Large hemorrhages are associated with varying degrees of dehydration, salt loss, lowering of blood pressure and hemoconcentration It has in addition been postulated that the reabsorption of digested blood from the gastrointestinal tract could directly influence protein metabolism⁶⁹

Often in hemorrhage, the problem is not one of blood loss particularly, for the quantity of blood lost may be considerably less important than the resultant degree of shock with fluid shunted from the active vascular circuit into stagnant depots Not to be overlooked is the starvation and fluid restriction that such persons are subjected to as part of the treatment of the bleeding

8 *Postoperative*

Case 8 One week before admission this 42 year old woman noted pain in both lower quadrants which increased in severity Anorexia and nausea developed, with some burning on urination

On physical examination tenderness and spasm of the lower abdomen were noted A doughy mass in the posterior cul-de-sac was palpable during the course of a painful rectal examination The temperature was 97° F, pulse 100 and respirations 25 The leukocyte count was 25,000 with 93 per cent polymorphonuclear neutrophils

The specific gravity of the urine was 1.020, a trace of albumin was present, a moderate number of leukocytes and a few coarse granular casts were seen in the sediment The non-protein nitrogen was 57 mg per cent

A laparotomy, performed two days after admission, disclosed a bilateral purulent salpingitis with peritonitis The fallopian tubes were removed and the abdomen drained Two days after operation the temperature rose to 101°, the pulse remained at 100, but the respirations rose to 30 On the eighth day the patient developed a generalized convulsion and thereafter frequent muscular twitchings were noted The non-protein nitrogen rose to 240 mg per cent, pain and swelling of the right parotid appeared, and the patient lapsed into coma and died

The autopsy revealed the presence of peritonitis and bilateral bronchopneumonia The combined weight of the kidneys was 395 gm The capillaries were engorged, the tubular epithelium swollen and, in places, desquamated Many of the tubules were distended with amorphous albuminous material and some of the lumina contained hyaline casts

Postoperative rises of blood non-protein nitrogen are extremely common if one performs routine blood chemistries This aspect of the subject has been recently discussed by Derow⁷⁰ The significance of insufficient fluid intake, lowered blood pressure, pituitrin medication, vomiting and increased body protein destruction was emphasized Not mentioned but of interest, is the possible presence of renal tubular damage which would add a local anatomic renal factor to the above mentioned impairments of physio-

logical functions Case 8 illustrates many of these mechanisms in a single patient Of note also in this case were the muscular twitchings which are classically seen in uremia

It is obvious from the data on hand that in all postoperative patients daily examination of the urine, with special reference to the 24 hour volume and specific gravity, should be performed Periodic blood chemical examinations would be of additional aid From these, one could detect an azotemia long before it became manifest clinically and could plan the therapeutic procedures more efficiently Pituitrin should be used with due caution

9 Congestive Cardiac Failure

Case 9 A 32 year old white man, admitted to the Boston City Hospital, had noticed progressive dyspnea, edema of ankles, cyanosis and a feeling of distress in his abdomen for 16 months The past history was not satisfactory Physical examination revealed a well nourished man, markedly cyanosed The peripheral veins were distended The lungs were free of rales The heart was enlarged, the pulmonic second sound was accentuated and a rough systolic murmur and thrill were noted over the apex The rhythm was regular and the pulse was 88 The blood pressure was 118 mm Hg systolic and 75 mm diastolic The liver was enlarged 6 cm below the costal edge and was tender There was soft pitting edema of legs, buttocks and sacrum

The urine contained an infrequent slight trace of albumin and 1 030 represented the maximum specific gravity The hemoglobin was 93 per cent (Sahli), erythrocytes numbered 5 5 million and the leukocytes 8,300

During the patient's hospital stay, the peripheral edema and cyanosis increased, the liver enlarged and eventually showed a systolic pulsation as did the distended neck veins The patient's condition grew steadily worse, and four days before death jaundice appeared which gradually increased in intensity The blood non-protein nitrogen on admission was 31 mg per cent but rose to 100 mg per cent two days before the onset of jaundice The blood pressure level was maintained until the end After a month, the patient sank into a deep coma and on the day before his death uremic snow was noted on the cheeks and sides of the neck The urinary output was diminished but the specific gravity remained at 1 030

The autopsy revealed rheumatic heart disease with mitral stenosis, tricuspid regurgitation and right ventricular hypertrophy Multiple pulmonary infarcts were present Chronic passive congestion of the liver, spleen and lungs was noted The combined weight of the kidneys was 285 gm The width of the cortex was 7 mm Microscopically the kidneys were normal except for congestion

Numerous studies of renal function during heart failure have been made^{71, 72} Foster⁷³ demonstrated that an increased non-protein nitrogen of the blood may result purely from circulatory disturbances In a study of eight cases of congestive heart failure he found an average non-protein nitrogen of 61 mg per cent with extremes of 40 and 90 mg per cent Four of these cases were examined after death and showed no evidence of renal disease

Sustained high venous pressure can cause congestion of the kidneys Even normal kidneys can accommodate for this congestion only to the limit of the distensibility of their capsules Congestion beyond this point pre-

sumably results in the compression of available space within the kidney, particularly the tubular lumina, eventually interfering with kidney function

The findings in Case 9 appear to justify a simple mechanical explanation of this sort. There was no change in blood pressure, no dehydration and no salt loss. This case, in addition, showed certain classic clinical features of uremia. The uremic frost was marked. The terminal stupor progressing to coma resembled that seen in organic kidney disease.

10 Intravenous and Transfusion Reactions

Case 10 A 46 year old man was admitted to Boston City Hospital, for treatment of an indolent ulcer of the left leg believed to be due to Buerger's disease. Previous admissions had revealed no findings of significance except those referable to partial occlusion of the arteries of both legs. The blood pressure had always remained about 130 mm Hg systolic and 80 mm diastolic. The renal function was normal. Physical examination on this admission revealed no new signs. The patient was treated by means of 200 c.c. of 5 per cent saline given three times weekly. He did well and after several weeks the ulcer began to heal.

A month after admission, following by one hour an injection of 5 per cent saline intravenously, the patient had a severe chill and began to vomit. The next morning jaundice was noticed. The pulse increased to 120 while the temperature rose to 103° F. The jaundice increased, the face and extremities became puffy, the conjunctivae chemotic, and hemorrhagic manifestations appeared. Significant changes in the laboratory data are tabulated in table 5. Unfortunately the presence or

TABLE V

	Blood Pressure		N P N	Sp Gr Urines	Urinary Volume	Icterus Index
	Systolic	Diastolic				
Before reaction	130	80	25 mg %	1.020	Normal	4
After reaction (only extremes tabulated)	140	80	155 mg %	1.028	Progressive diminution to complete anuria	100

absence of hemoglobinuria was not ascertained. The liver was slightly palpable. Repeated blood cultures showed no growth. The patient continued on a progressively downhill course, developed anuria, lapsed into coma and died five days after the onset of the reaction. The postmortem examination revealed a normal sized liver with scattered areas of necrosis, atherosclerosis of the peripheral arteries and terminal bronchopneumonia. Blood cultures were negative. The combined weight of the kidneys was 540 gm. The cortex was 1.2 cm wide. Microscopically there was no evidence of vascular or glomerular involvement. The convoluted and collecting tubules contained granular material. The tubular epithelium was somewhat flattened.

This bizarre clinical picture resembles closely that reported in other instances as following certain transfusions^{74, 75}. Hench⁷⁶ reported a quite similar reaction following the intravenous injection of typhoid vaccine. This naturally raises the question as to whether some common mechanism underlies these seemingly isolated types of reactions.

An analysis of the above case shows that salt loss, dehydration and hypotension were not operative here. Liver damage was not sufficient to be a factor. Excessive protein catabolism alone could scarcely be responsible for a rise of blood non-protein nitrogen to 155 mg per cent. The kidneys showed evidence of tubular damage and much debris blocking the tubular lumina. It thus seems that the local renal factor was most important here.

This appears to agree with the results secured by DeGowin et al.⁵² in explaining a similar syndrome due to blood transfusion reactions. These workers showed that in acid urine, the excretion of hemoglobin caused obstruction of the tubular lumina with masses of pigment derived from hemoglobin. Unfortunately, in our case, no search for hemoglobinuria was made. The hemolysis of blood caused by the injection of any deleterious substance would allow us to explain these reactions on a mechanism similar to the one proposed by DeGowin et al.⁵² Further study is obviously needed.

11 *Weil's Disease*

*Case 11** A 38 year old man was admitted to the Boston City Hospital severely prostrated and jaundiced. For one week, weakness, muscle pains, prostration, chills, vomiting and progressive jaundice had been noted. Physical examination revealed severe icterus, moist râles in the chest, hemorrhagic herpes of the lips, mucous membrane bleeding, a distended abdomen and tender thigh muscles. Blood pressure was 120 mm Hg systolic and 50 mm diastolic.

The urine was highly concentrated, and contained albumin and many granular casts. There was a leukocytosis of 28,700. The non-protein nitrogen of the blood was 200 mg per cent, the sugar 55 mg, the cholesterol 90 mg and the total protein 4.4 gm per 100 cc. The blood phosphorus was 13.6 mg and the calcium 10 mg per cent. The patient lapsed into coma and died 16 hours after admission.

The postmortem findings were typical of Weil's disease. The combined weight of the kidneys was 530 gm. The cortex was 8 mm wide. Microscopically, interstitial infiltration of a multicellular type was noted, for the most part in the medulla. Some of the tubules were dilated and their epithelium showed evidence of regeneration. In certain tubules granular debris was present. In about a fourth of the convoluted tubules there was swelling of the epithelial cells with narrowing of the lumina. Spirochetes were found in the convoluted tubules.

Azotemia is constantly present in the second stage of severe cases of Weil's disease.⁷⁷ In mild cases it may be absent. It is well known that tubular damage and blocking of the renal tubules by granular debris are commonly present in this disease. In view of the close similarity between Weil's disease and yellow fever, one must not overlook the possibility of liver damage contributing to the azotemia. This has been shown to be so for yellow fever.³⁸ Dehydration is in addition common. The tubular changes must be considered reversible, since the patients who recover regain entirely normal renal function.

12 *Addison's Disease*

Case 12 A 12 year old girl was admitted to the Evans Memorial Hospital in a moribund state. For six months she had had progressive fatigue, weakness, anorexia,

* This case was previously reported in detail.⁷⁷

vomiting, weight loss, cramp-like pains in the abdomen and legs, and bronzing of the skin. Physical examination revealed prostration, emaciation, bronzed and pigmented skin and mucous membranes. The pulse was 108, the blood pressure was 74 mm Hg systolic and 44 mm diastolic.

The blood sugar was 68 mg per cent and the non-protein nitrogen 120 mg.

The postmortem findings were consistent with the clinical diagnosis of Addison's disease, both adrenals showing marked atrophy. There was no evidence of tuberculosis. The combined weight of the kidneys was 225 grams, they showed no gross changes. Microscopically there was no evidence of vascular or of glomerular disease. There were slight engorgement and edema with some lymphatic infiltration. About one-third of the tubules showed swelling of the epithelium, with eosinophilic cells and pyknotic nuclei. Some of the lumina were filled with granular debris.

Marshal and Davis⁷⁸ first pointed out the occurrence of a rise in the non-protein nitrogen of the blood following adrenalectomy. This was also found fairly consistently by Rowntree⁷⁹. Later Loeb and his co-workers^{80, 86} demonstrated the urinary loss of sodium associated with adrenal insufficiency. This loss of sodium, chiefly as chloride, was then confirmed by other workers. It was suggested that the adrenals probably exert a regulating influence on body sodium.⁸⁶

Other factors besides this loss of sodium influence the elimination of non-protein nitrogen from the blood in Addison's disease. The loss of sodium chloride is associated with varying degrees of dehydration. Also the typical asthenia of this disease is associated with a progressive lowering of the blood pressure. As already discussed in this paper, Loeb et al.⁸⁶ have suggested that the lack of the adrenal cortical substance acts specifically to cause urea retention in the blood stream.

In view of this patient's youth and lack of history of renal disease it was felt that this case was of particular interest here. This viewpoint was justified by the minimal degree of renal damage seen at autopsy. All changes are confined to the tubules, only about a third of which were involved and those only to a degree which would generally be termed moderate.

13 *Pneumonia*

Case 13 A 45 year old negro was admitted to the Boston City Hospital, complaining of cough and dyspnea. He had been well until five days before when he had a chill, and subsequently began to cough and raise small amounts of whitish sputum which was sometimes blood-streaked. There was no chest pain. He had been perspiring profusely during the past four days. There was no history of previous renal disease.

On physical examination of the chest signs of consolidation were found in the upper portion of the right lung and in the base of the left lung. The blood pressure was 110 mm Hg systolic and 60 mm diastolic. The temperature was 103° F, pulse 140 and respirations 50.

The urine had a specific gravity of 1.014, contained albumin but no casts or pus cells. The hemoglobin was 86 per cent, the leukocyte count 10,800. A type V pneumococcus was obtained from the sputum and blood. The non-protein nitrogen was 70 mg per cent.

The patient's condition grew rapidly worse and he died two days after admission.

The autopsy revealed the presence of lobar pneumonia of the right upper and left lower lobes with extension to all remaining lobes. The combined weight of the kidneys was 360 grams. The width of the cortex was 0.5 cm. Microscopic studies showed minor degrees of tubular damage. The glomeruli appeared normal. Some of the tubular lumina contained granular debris.

In view of the discordant results of earlier investigations, Farr and Abernathy⁸¹ carefully studied the renal function in 28 cases of pneumonia. The urea clearance test indicated an actual increase in this type of renal function in the pre-critical stage of the disease particularly in the younger age group (i.e. up to an age of 40). They concluded that in the pre-critical phase of pneumonia renal function may be elevated, unchanged, or slightly impaired. In general they noted that the level of renal activity was inversely proportionate to the age of the patient.

Of particular interest are two cases in their series which exhibited high blood urea nitrogen values on admission, with low urea clearance, both of which returned to normal during the next few days. It was felt that these patients were probably dehydrated and that extrarenal factors played a dominant rôle in the production of these changes.

The occurrence of hypochloremia during the course of lobar pneumonia has been recognized for some years⁸². Several workers have found the sodium to be diminished as well⁸⁵. Low total base values have likewise been reported⁸⁵. More recently, Atchley⁸³ has brought forth the conception that a shock-like state exists in pneumonia, with accompanying dehydration, and hemoconcentration⁸⁴.

To go one step further, it has been noted that, with various infectious diseases including pneumonia, it is not unusual to find hemorrhagic necrosis of the adrenals post mortem⁸⁷.

In summary, then, increased protein catabolism, dehydration, electrolyte disturbance, lowered blood pressure and toxic damage to the adrenals and kidneys are significant factors in producing azotemia in pneumonia.

Case 13 is illustrative of azotemia in pneumonia. It was not well enough studied to permit critical evaluation of the factors responsible. At autopsy the evidence of renal tubular damage was striking.

14 *Allergy*. Rackemann, Longcope and Peters⁴⁷ in 1916 confirmed the fact that in serum disease there was often a marked but transient retention of chlorides and of water, associated frequently with albuminuria, cylindruria, and sometimes with impaired phenolsulphonephthalein excretion. The kidneys in these cases showed an impaired ability to eliminate chlorides and loss of power to concentrate urine. The following year Longcope and Rackemann⁸⁶ reported two interesting cases of azotemia associated with attacks of urticaria. In each case with the onset of the acute allergic state, albumin and casts appeared in the urine, the phenolsulphonephthalein excretion diminished and the blood non-protein nitrogen rose (in one instance the blood urea nitrogen reached a level of 290 mg per cent). Plasma chloride values were low. Even with so high a degree of nitrogen reten-

tion as that mentioned, the patients recovered rapidly and completely. The cases were not studied from the viewpoint of this paper and therefore the exact mechanism responsible is not clear. There seems little doubt that allergic states can produce an azotemia of extrarenal origin.

15 *Diabetes Mellitus* Many clinicians and investigators are aware of the frequent association of diabetic coma and azotemia⁸⁷. This is often erroneously attributed to kidney disease.

Peters et al.,⁸⁸ in a study of the total acid-base equilibrium in diabetics, called attention to (1) the loss of fluid because of glycosuria, polyuria, base excretion and vomiting, (2) loss of base bound to ketones which are thus excreted in the urine, and (3) the availability of base released from chloride for ketone neutralization. It was pointed out that the result is a state of dehydration and salt depletion as well as acidosis. Atchley and Benedict⁸⁹ arrived at similar conclusions. The dehydration causes a decrease in blood volume with consequent decrease in blood pressure and increase in the percentage of blood proteins.

McCance and Lawrence⁸⁷ reviewed the proposed mechanisms supposedly explaining the production of extrarenal azotemia in diabetic coma and concluded that no proposed mechanisms including dehydration, failing circulation, low blood pressure, excessive protein catabolism, action of insulin, ketosis and salt depletion could be invariably and wholly responsible for the extreme and consistent degrees of nitrogen retention which occurred in some of their cases. These authors believe that another mechanism must be present. They point to the similar occurrence of nitrogen retention in Addison's disease and conclude that the causes may be similar, that is a deficiency in fixed base which may be brought about not merely by acidosis and diuresis but possibly by a partial failure of the suprarenal cortex.

16 *Shock* Moon⁹⁰ has been able to show that the advanced stages of shock are invariably associated with an increased blood non-protein nitrogen. Drop in blood pressure and loss of circulating blood volume seem to be the chief factors concerned. Moon⁹⁰ lists a large group of diseases in which severe shock (and therefore azotemia) occurs. Blood is lost by being shunted into stagnant depots. Also, changes in capillary permeability cause loss of fluid and electrolytes into interstitial tissues.

17 *Acute Pancreatitis* DeTakats and Mackenzie⁹¹ recorded a case of pancreatitis with azotemia. They expressed the view that it would commonly be found if examinations of the blood chemistry were routinely performed in this disease. The same mechanisms used to explain azotemia in shock probably apply here.

18 *Diantheal Diseases* As one would expect, fluid and salt loss are the chief initiating factors⁹². Not to be overlooked are fever, starvation, and infection, all of these can increase protein catabolism. With severe dehydration the blood pressure falls. Toxic damage to kidney tubules may occur.

19 *Heat Cramps* Talbott⁹³ has demonstrated that in heat cramps the

blood sodium and chloride are diminished. Hemoconcentration and azotemia are constant features. The disease is initiated by excessive loss of sodium chloride in the sweat. Here is an interesting example of dehydration due to sodium loss. In most cases these persons continued to drink water which is, however, of no avail until the sodium chloride loss is replaced.

20 Drug Intoxication A few drugs seem to affect nitrogen metabolism. Of these, the iodides are probably the most outstanding. Grabfield and his co-workers⁴⁹ showed that the continued use of potassium and sodium iodides may cause an increase in the output of nitrogen in the urine. Potassium iodide particularly may cause an increase in the blood non-protein nitrogen, amounting sometimes to 30 per cent of normal values and occasionally reaching abnormal figures. These results were attributed chiefly to an increased rate of protein catabolism. The possible deleterious effect of potassium on kidney function must not be forgotten.

Of the chemicals and poisons which may affect kidney function indirectly, phosphorus and chloroform³⁷ are the most common. If the kidneys are not directly involved, azotemia may result because of liver cell destruction, and consequent loss of the ability of the liver to deaminate amino acids. An increased rate of protein catabolism may be present. More often than not, actual renal insufficiency supervenes, and the blood urea nitrogen increases in relation to the increasing urea threshold in the kidney.

21 Burns The relation of superficial burns to azotemia is important. In 1923 Underhill and his co-workers⁹⁴ demonstrated that many of the constitutional effects of extensive burns were due to the presence of marked hemoconcentration. This was borne out by the fact that improvement followed in most instances when the normal blood volume was restored.

At about the same time Robertson and Boyd⁹⁵ stressed the factors of primary shock occurring in those cases which terminated fatally within the first 24 hours, and toxic shock which resulted in a later death. The latter very likely is what is now recognized as the syndrome of hemoconcentration.⁸⁴

Later Davidson⁹⁶ in studying the sodium chloride metabolism of patients suffering from burns found a significant lowering of the blood chlorides. In general, the disturbance of chloride metabolism was proportionate to the amount of devitalized tissue. Davidson also believed that an increased rate of protein catabolism accompanied lesions of this sort.

Recent investigators have focused their attention sharply on sodium metabolism and the adrenal glands.⁵⁷ As evidence accumulates it seems more and more probable that adrenal hormonal regulation with control of sodium metabolism and restriction of urea excretion may be a basic factor in conditions of this type. The presence of pathological changes in the adrenals noted at postmortem examinations of patients who have died as a result of severe burns would appear to give added weight to this point of view.⁵⁷

In summary then the lowered blood pressure, increased protein catabolism, hyponatemia and hypochloremia, dehydration and toxic damage to the adrenals are chiefly responsible for the azotemia found in burns

CLINICAL PICTURE OF EXTRARENAL UREMIA

The clinical picture of the classical type of uremia due to organic kidney disease has been well reviewed by Fishberg⁹⁷ and more recently by Harrison and Morton⁹⁸ Fishberg⁹⁷ defines uremia as "a complex autointoxication, the variegated clinical picture being the summation of the effects of retention of various urinary constituents, largely, it would seem, end-products of protein catabolism" He further remarks "no group of symptoms is to be considered as uremic in nature unless it occurs in the presence of abnormally high non-protein nitrogen in the blood"

The mechanisms described in this paper can undoubtedly cause the retention of other substances besides the nitrogenous waste products This would fulfill the requirements of the above definitions Harrison and Morton⁹⁸ state that the syndrome of prerenal azotemia resembles true uremia in both its chemical and clinical aspects

True uremia will always be found a concomitant part of the clinical picture of organic renal failure Since few renal diseases are fulminating, the symptoms are often present for weeks or months

Extrarenal uremia, on the other hand, must of necessity be superimposed on the clinical features of many widely varied and entirely unrelated diseases Further, the diseases which cause this type of uremia are usually acute and fulminating, their duration being one of days For this reason the clinical manifestations of chronic uremia (i.e. yellowish pallor of the skin, pericarditis, uremic colitis with diarrhea, severe anemia, extreme dryness of the skin, uremic eruptions and emaciation) are but rarely seen The chief features of extrarenal uremia seem to be fatigue and drowsiness, progressing into stupor and coma within a period of a day or longer Case 9 in our series showed the classical deposit of uremic crystals on the skin Case 8 presented muscular twitchings What should be particularly emphasized is that we lack a careful chemical analysis of cases falling into this group and that such a study is needed in order to define more clearly the clinical picture of extrarenal uremia Whether the non-excretory functions of the kidneys are affected in this syndrome to a degree sufficient to be clinically detectable is at present not known Snapper⁹⁹ believes them important in explaining uremia

ANURIA

One hears only too frequently such expressions as "the patient's kidneys have closed down, the patient has developed reflex anuria, etc" Even more unfortunate is the fact that many physicians treat all oliguric and anuric patients in a routine fashion without attempting to evaluate properly and specifically treat the factors responsible for the diminished or absent kidney

function. It is evident that the problem of anuria is closely linked with the problem of azotemia. Essentially, anuria may be looked upon as an exaggerated degree of oliguria. Therefore, a discussion of the mechanisms involved in the production of anuria will clarify both subjects.

The most satisfactory working classification of the anurias is that which divides them into one of the following categories: (1) Prerenal, (2) Renal and (3) Postrenal.¹⁰⁰

Prerenal In prerenal anuria the causative factors lie outside of the kidneys and genito-urinary tract. It is immediately evident that this type of anuria represents but a severe degree of several of the mechanisms previously discussed, that a drop in blood pressure sufficient to nullify the intraglomerular pressure will produce anuria, and that severe degrees of dehydration and sodium chloride deficiency may also produce anuria.

The existence of reflex anurias has been disputed. That splanchnic stimulation can diminish urinary function is well established. The usual reflex anuria means complete cessation of function in one kidney following some catastrophe to the other.¹⁰⁰ It has been suggested also that stimuli to the renal splanchnics may arise from nerve insults outside of the renal system causing an inhibition of function of all renal tissue. Such a mechanism if it exists must be included with the prerenal group of anurias. It would explain anuria following such widely varied events as immersion in cold water, hysteria, and operations on organs distant to the genito-urinary tract. Of interest is Cubitt's statement³ that most case reports in which reflex anuria has been postulated do not contain blood pressure measurements nor facts relating to other mechanisms controlling renal function.

Renal Anuria Renal anuria refers to factors operating primarily within the kidney. In addition to diffuse inflammatory lesions, chemical damage, neoplastic invasion, mechanical destruction, removal, congenital defects and degenerative changes, one must also include edema of the kidneys due to venous congestion or tubular occlusion due to nephrotic changes. These latter two have already been discussed under local conditions causing azotemia. When of severe degree they can readily produce anuria.

Postrenal Postrenal anuria refers to the type due to mechanical factors causing obstruction to the outflow of urine. These are either bilateral or unilateral and in the latter instance may be associated with reflex anuria or subnormal renal function of the opposite kidney.¹⁰¹ The majority of the cases falling in this category are due to ureteral calculi or strictures or to urethral obstruction. Where the possibility of this type of anuria exists the patient should be studied intensively by urological methods.¹⁰¹

Discussion The foregoing classification allows a more rational approach to the problem of anuria. It is evident that an understanding of the mechanisms involved clarifies the study of any particular case. By discarding obscure and complicated classification dependent primarily on the relationship between anuria and a wide and varied number of systemic con-

ditions, one's attention is necessarily focused on the few fundamental mechanisms involved in the production of anuria

The treatment of anuria will necessarily depend on the primary disturbance by which it is produced. If obstructive lesions of the genitourinary tract and intrinsic renal disease are ruled out, the remaining mechanisms which produce anuria are the same as the mechanisms discussed under the production of prerenal and functional azotemia, and should be treated in a similar fashion

METHODS OF DIFFERENTIATING AZOTEMIAS

Since the mechanisms producing azotemia are numerous, it is evident that a somewhat elaborate diagnostic study of cases of unexplained azotemia will be necessary. The first consideration in explaining any azotemia should be the investigation of whether true organic renal disease, or the mechanisms discussed in this paper are responsible

Renal lesions which produce true uremia, as a rule, cause changes in the urine distinct from those seen in functional azotemia. Fishberg comments on this fact⁹⁷. In true uremia the specific gravity is usually fixed at a low level, often 1.010, and only rarely as high as 1.015. In sharp contrast is the specific gravity of the highly concentrated urine of functional azotemia which may range as high as 1.040. Exceptions to this are some of the cases with severe tubular damage as a complication to the extrarenal factors. Here the specific gravity may be lower. These changes, however, develop far more rapidly than in the usual organic renal diseases.

The volume of urine is not so important since it may be diminished in both types. It is evident that the finding of albumin, casts and cells in sediment is often of little differential value. The general clinical picture will probably be the most important aid in determining whether or not organic renal disease is present.

If it is believed that azotemia is of the type discussed in this paper an effort should be made to determine which of the basic mechanisms is present. This may entail detailed laboratory study of the case, but since functional azotemia is frequently reversible, a knowledge of the causative mechanisms will often point to therapy which may prove life saving.

From this point of view the minimum information needed would include. The systemic arterial blood pressure, 24 hour fluid intake and urinary output, measurement of fluid lost by extrarenal channels, urinary specific gravity, presence or absence of ketonuria, blood sodium, blood chloride, carbon dioxide combining power, total blood protein, erythrocyte count, hemoglobin, hematocrit value, and blood non-protein and urea nitrogen. If the patient has liver disease a nitrogen partition of the blood should be performed including the amino-acid nitrogen. In the case of congestive heart failure or obstruction of the inferior vena cava, the venous pressure obtained in the femoral vein would be of value. The factor of protein cata-

bolism could only be resolved by complete nitrogen studies such as would be impractical for routine clinical use

With dehydration various constituents of the blood increase in addition to the non-protein nitrogen. Since the blood urea content does not increase in proportion to the loss of fluid, it is evident that the degree of dehydration cannot be determined from the level of the total non-protein nitrogen or any of its constituents. A much better criterion of the degree of dehydration is the increase of total blood protein, erythrocyte count, hemoglobin or hematocrit value. The simplest to use, and probably the most accurate, is the hematocrit value (volume per cent of erythrocytes per 100 c c of blood). A single reading (unless well over normal) is not nearly so valuable as serial studies. By this means, the progression or regression of the dehydration can be quantitatively determined. If there is a possibility of the patient having an anemia or blood loss the total blood proteins could be substituted with advantage.

Blood sodium and blood chlorides should be determined separately, if possible. Few laboratories are equipped to perform routine sodium determinations at present. As previously pointed out, chloride and sodium levels do not always parallel each other. When only blood chlorides are determined, this fact should be kept in mind.

Indirectly, the sodium level can be roughly surmised in many cases from a comparison of the blood chloride level and the carbon dioxide combining power. If the carbon dioxide combining power is high (alkalosis) and the blood chloride level is low, then the sodium level is probably near normal. Conversely a low carbon dioxide combining power (acidosis) with normal or slightly low blood chloride level speaks for the presence of an hyponatremia. This knowledge aids greatly in treating the disturbed electrolyte and fluid balance.

TREATMENT

Rational therapy in instances of this syndrome is necessarily dependent on the determination of the fundamental mechanisms responsible for its production. Due consideration must also be given to the underlying disease process, specific therapy of which may occasionally be available.

In many cases the factors of dehydration and salt deficiency are coincident. The fluid needs of the patient can be roughly calculated from the following program suggested by Collier and Maddock²⁶. The fluid intake should be sufficient to (1) furnish 1500 c c of urine daily, (2) replace abnormal fluid losses such as vomitus, drainage from fistulae, diarrhea, etc., and (3) replace water of evaporation from skin and lungs which amounts to 1000 to 1500 c c daily in uncomplicated cases. With increased heat production, fever, high basal metabolic rate or sweating in hot and humid environments, this loss may amount to 1500 to 3000 c c of fluid per day.

An initial infusion amounting to 6 per cent of the total body weight may safely be given at the beginning of serious dehydration²⁶. Normal saline

is the fluid indicated in most cases. If the patient should be dehydrated, but not suffering from salt loss, 5 per cent glucose in distilled water could be utilized. In severe alkalosis (where the blood sodium is near normal and the chlorides markedly depressed) normal saline may at times fail to correct the electrolyte disturbance. Under such circumstances fluid should be given as isotonic glucose in distilled water and the chlorides supplied by means of ammonium chloride, calcium chloride or even hydrochloric acid. In severe acidosis, where the hyponatremia exceeds the hypochloremia, part of the sodium deficit can be supplied as sodium lactate solution.¹⁰² Where the salt loss greatly exceeds the fluid loss (i.e. in Addison's disease, toxic adrenalitis) it may be necessary to give sodium chloride in addition to that present in physiologic saline. Large oral doses or injection of hypertonic salt solutions is then indicated. Root¹⁰³ calls attention to the fact that anurias which fail to respond to injections of normal saline may do so after the use of hypertonic salt solution.

Fluids may be given orally, intravenously or hypodermically. If the latter method is used, the isotonicity of blood should not be exceeded. It is impossible to give sufficient fluid by rectal instillation alone, although this method can be used to supplement other procedures. Often overlooked is the possibility of giving large volumes of fluid by means of a Levene tube passed into the duodenum and left in place.¹⁰⁴ Some authors believe this to be a better method than the intravenous route.¹⁰⁰ It has the great advantage that nutrient foods can be added to the infused fluid.

In the event of a high non-protein nitrogen due to liver disease the intake of carbohydrates should be increased and the fat and protein diminished. At least 400 grams of carbohydrate are needed daily.

If starvation has been present the protein requirements should be satisfactorily met. Glucose therapy is indicated when acidosis is present.

Where high venous pressure is a factor, specific cardiac therapy and possibly venesection would be of value.

The maintenance of a systolic blood pressure greater than 70 mm of Hg is desired. Blood pressures below this level are usually associated with collapse and shock which must be vigorously treated. The restoration of the normal circulating blood volume will entail intravenous injections of saline, glucose or blood. The patient should be put in "shock position," heat artificially supplied, and oxygen therapy instituted. Strychnine, caffeine, coramine, cardiazol, ephedrine and benzedrine are among the drugs which may be of value. Weiss and Wilkins¹⁰⁵ have recently discussed this aspect of the subject at length.

Where adrenal damage is suspected, and certainly in Addison's disease, the use of adrenal cortical hormone should not be overlooked.¹⁰⁶

In spite of these medical procedures, patients may at times show a progressive increase in azotemia and oliguria, terminating in anuria. This is often due to tubular damage, edema of the kidney or possibly to reflex anuria. There seem to be two surgical procedures which at times may be

valuable. Some striking cures have been reported. The chief obstacle to their use seems to be the lack of any clear cut criteria as to when they are indicated. Few physicians have had any experience with them.

The simplest, and to be tried first, is the sectioning or blocking of the renal sympathetics. This can be done by paravertebral injection of a local anesthetic.¹⁰¹ Cubitt³ has reported excellent results in reflex anuria by the simple procedure of spinal anesthesia. Milliken and Karr⁵¹ favor the use of periaortic sympathectomy.

Where swelling of the kidneys exists bilateral decapsulation may be life saving. Dunn and Dunn¹⁰⁷ have reviewed this subject and offer a remarkable example of such a cure. Such radical procedures should be attempted only under the guidance of an experienced internist and genito-urinary surgeon.

Besides replacement and supportive therapy, every effort should be made to prevent undue loss of fluid and electrolytes. This may mean operation in the case of pyloric obstruction, coagulant therapy in the case of superficial burns, change of environment in the case of excess sweating, repair of fistulae, treatment of diabetes mellitus to relieve polyuria, etc. Such treatment of the underlying disease may prevent the factors causing azotemia from continuing to act. Therapy to relieve azotemia should never be considered to the neglect of such treatment of the underlying disease.

DISCUSSION

To many physicians an elevated blood non-protein nitrogen means kidney disease. It has been our experience on several occasions to meet surgeons who refused to operate on persons with an obstructed pylorus or peritonitis because of an azotemia and the presence of albumin and casts in the urine. These patients were diagnosed as having "kidney disease" or "nephritis" and therefore considered poor operative risks. Such a view is of course not tenable. In routine clinical practice, an azotemia is much more commonly due to the mechanisms discussed in this paper than to organic renal disease. At present, non-protein nitrogen determinations are rarely performed except for persons suspected of having renal disease. Routine and serial blood chemical studies for all the diseases mentioned previously would undoubtedly reveal a striking number of instances of azotemia.

Another common misconception is that the level of the blood non-protein nitrogen in extrarenal azotemia rarely increases to a degree comparable with that seen in organic renal disease. Quite the opposite is true. Values of 100 or even 200 mg per cent are common. Not only may such high figures be observed but frequently they develop within a few days and may disappear as rapidly, if the patient's underlying disease is amenable to treatment. Fishberg⁹⁷ mentions a patient with prerenal azotemia in which the blood non-protein nitrogen increased to 400 mg per cent in three days and diminished in an equally striking fashion following therapy.

The ubiquity of this syndrome should be kept in mind. There are few specialties in which it will not at some time be encountered.

It is hoped that this presentation will aid in clarifying the clinical concept of extrarenal azotemia, though the problem still presents numerous questions to be solved. It is a subject which deserves more attention from the medical profession and which should not be neglected in presenting the problem of renal disease to medical students.

CONCLUSIONS

The syndrome of extrarenal azotemia is present in a wide variety of unrelated and often common diseases. The basic mechanisms producing this syndrome have been analyzed and include (1) Fall in blood pressure, (2) hypochloremia and hyponatremia, (3) dehydration, (4) increased protein catabolism, (5) loss of deaminizing power of the liver, and (6) local renal factors. Reasons are given why cases with tubular damage or edema of the kidney should be included in this syndrome. These mechanisms are interdependent and interrelated and present in varying combinations in different diseases. The relation of the anurias to this syndrome is discussed. Diseases associated with azotemia have been analyzed with this concept in mind. Methods for evaluating the syndrome and consequent procedures for logical treatment have been presented.

Note. Since the preparation of this paper several interesting and pertinent contributions have appeared in the literature. In continuing the search for a toxic substance elaborated in instances of high intestinal obstruction, Scudder, Zwemer and Truszkowski (Surgery, 1937, 1, 74) demonstrated experimentally a resulting rise in blood potassium which attained definite lethal proportions. This suggests the need for further study of the potassium factor in extrarenal uremia. Gomori (Acta med Scandinav, 1937, xii, 497, 503, 515, 1937, xciii, 42) has produced considerably more evidence to substantiate his original views on extrarenal azotemia. Wohl and his co-workers (Jr Lab and Clin Med, 1938, xxiii, 450) have brought forth experimental and clinical data indicating that adrenal damage is often associated with instances of uremia of the extrarenal type. Indeed, as our knowledge of this syndrome increases, the importance of the adrenals becomes more and more impressive. In an exhaustive paper on acute renal pathology, Bell (Am Jr Path, 1937, xiii, 497) has included findings in certain cases in which extrarenal factors had been present. These consisted chiefly of distortion of the convoluted tubules with minor degenerative changes in their lining cells. The influence of these minor pathologic changes on renal function are discussed.

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CASE REPORTS

LARGE PERICARDIAL EFFUSION COMPLICATING ACUTE CORONARY THROMBOSIS^{*}

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THE clinical features of the pericarditis found during the course of some cases of acute coronary artery thrombosis have been recently reviewed by Blumer¹ who rejuvenated the term *pericarditis epistenocardica* first applied to this condition in 1910 by Sternberg.² In 1872 Baumes³ gave the first clinical picture of *pericarditis epistenocardica*, though he was not aware of the relation of the condition he described to acute coronary artery thrombosis and in fact dubbed the pericarditis "idiopathic." He called attention to the absence of pericardial effusion in his cases. White⁴ comments on the infrequency of pericardial effusion following coronary thrombosis and avers it is of no clinical significance. Levy⁵ states he has never seen effusion in detectable amount associated with coronary thrombosis but in a footnote relates that Herrick has seen one case. Levine⁶ in his recent monograph on heart disease says "Only on very rare occasions is pericardial effusion associated with this type of pericarditis" but does not cite a case in his own experience. Schwartz,⁷ in 1934, was the first to record the clinical detection of pericardial effusion following acute coronary occlusion, his case being that of a man of 50 years who improved after pericardial paracentesis and eventually recovered. Master and Jaffe⁸ reported the following year two cases, both of whom recovered without pericardial paracentesis. These authors believe that pericardial effusion of similar origin must be less rare than the clinical reports published make it appear. The present case is of interest because the effusion was of enough volume to make paracentesis an essential therapeutic procedure and also because following recovery a carcinoma of the cecum was successfully removed.

CASE REPORT

Mr. E. D., a white male of 64 years, with previous good health except for constipation, slight anemia, occasional dyspnea on climbing stairs, and one attack of angina of effort, was stricken on the night of March 6, 1935, with heavy substernal oppressive pain which radiated to the left arm and lasted several hours, relief being obtained only after 30 mg. morphine sulfate were given hypodermically by his physician. Weakness and sweating followed the pain. He was kept at rest, but three days later had a similar attack severe enough to again require 30 mg. of morphine sulfate for relief. The blood pressure was 95 mm. of Hg systolic and 60 diastolic, the pulse weak and the skin moist and cool. The temperature rose during the next few days to 100° F. and a pericardial friction rub was heard on the seventh day, by which time the diagnosis of acute coronary artery thrombosis seemed well established although an electrocardiogram and leukocyte count were lacking. The low grade

^{*} Received for publication July 2, 1937.

fever terminated on the twelfth day, after which time the patient was fairly comfortable until the seventeenth day when the temperature rose to 101° F with the advent of mild substernal pain. He then became weaker and complained of pains through the left chest, so by the end of the third week of his illness, on the occasion of my initial visit, he appeared distressingly ill, was mildly cyanosed and orthopneic. The temperature was 102° F, the pulse soft, rate 124, with sinus arrhythmia, and the blood pressure was 98 systolic and 70 diastolic. Increased venous pressure was indicated by venous pulsation in the neck veins when in the erect position, but no direct measurement was made. The left border of cardiac dullness by percussion extended to the anterior axillary line at the sixth interspace, and the right border was 1 cm beyond the right sternal margin. The apex beat was not located and the heart sounds were somewhat indistinct. There was dullness at the left lung base, with exaggeration of breath sounds, and moist rales at both bases. The liver edge was 3 cm below the right costal border and there was moderate edema of the ankles.

The diagnosis of pericardial effusion following coronary artery thrombosis was suggested. An *electrocardiogram* (3-28-25) revealed slight depression of the RS-T segments in Lead I, with T₁ slightly positive, while conversely in Lead III there were slightly elevated and coved RS-T segments and inverted T-waves. T₂ was inverted. Q and Q₃ were prominent. In Lead IV there was definite elevation of the RS-T segment, and the T-waves did not dip below the isoelectric level. These changes were considered fairly typical of a late Q₃T₃ pattern (this record was made three weeks after the initial episode) indicating infarction, probably in the posterior basal portion of the left ventricle. (Sections of this and subsequent electrocardiograms are depicted in figure 1.)

The hemogram showed red blood cells 3,300,000, white blood cells 9,650, hemoglobin 60 per cent. Neutrophils were 83 per cent, lymphocytes 14 per cent, mononuclears 3 per cent. The blood Kahn and Mueller tests were negative. There were 30 mg non-protein nitrogen and 1.5 mg creatinine per 100 c.c. of blood. A urinalysis was normal.

Radiographic examination (figure 2-A) showed marked general enlargement of the "cardiac" shadow, even after allowing for distortion due to the semi-recumbent position of the patient and a target distance of only 30 inches, and the size and contour were considered suggestive of pericardial effusion. The lung fields showed the changes typical of congestive failure, but otherwise were negative.

Since it was felt that *Heinz-tamponade* accounted for a good part of the patient's discomfort, a needle was inserted below the angle of the left scapula in the seventh interspace and 500 c.c. of amber thin fluid were withdrawn freely from the pericardial sac. The fluid showed 20-35 erythrocytes per field and only 1-3 leukocytes, with lymphocytes predominating on the stained smear. Cultures of the fluid were free from growth after seven days incubation. The improved "cardiac" contour two hours after the paracentesis is shown in figure 2-B, but part of the change was due to the more erect position of the patient and to the fact that this roentgen-ray was made at a distance of 5 feet. The measurements were total transverse "cardiac" diameter 18.5 cm, M R 9 cm, M L 9.5 cm, and internal diameter of chest 30 cm, giving a cardio-thoracic ratio of 60.1 per cent. An *electrocardiogram* made the following day (3-29-35) showed no significant change from the previous record.

Following the pericardial paracentesis the patient was greatly relieved, but owing to the evident congestive failure oxygen therapy, 50 per cent dextrose solutions intravenously and digitalis were employed. The rate of improvement was strikingly indicated when the patient remarked only 12 hours after the paracentesis that "he felt like a new man." The fever disappeared within 48 hours and the following day a direct venous pressure reading was only 10 cm of water. The heart gradually slowed, the blood pressure ranged from 100 systolic and 60 diastolic to 120 systolic

and 80 diastolic, and all signs of congestive failure cleared up at the end of a week. An *electrocardiogram* at this time (4-5-35) showed no essential change.

A small, slightly tender mass was discovered in the right lower quadrant of the abdomen and occult blood was found in the stools. Roentgen-ray examination of the colon revealed a "napkin ring" defect just above the ileocecal valve diagnosed as carcinoma of the cecum.

Improvement in the circulatory state was continuous. A teleoroentgenogram taken five weeks after the paracentesis, on May 11, 1935, showed further decrease in the "cardiac" size, the total transverse "cardiac" diameter measuring 16.5 cm,

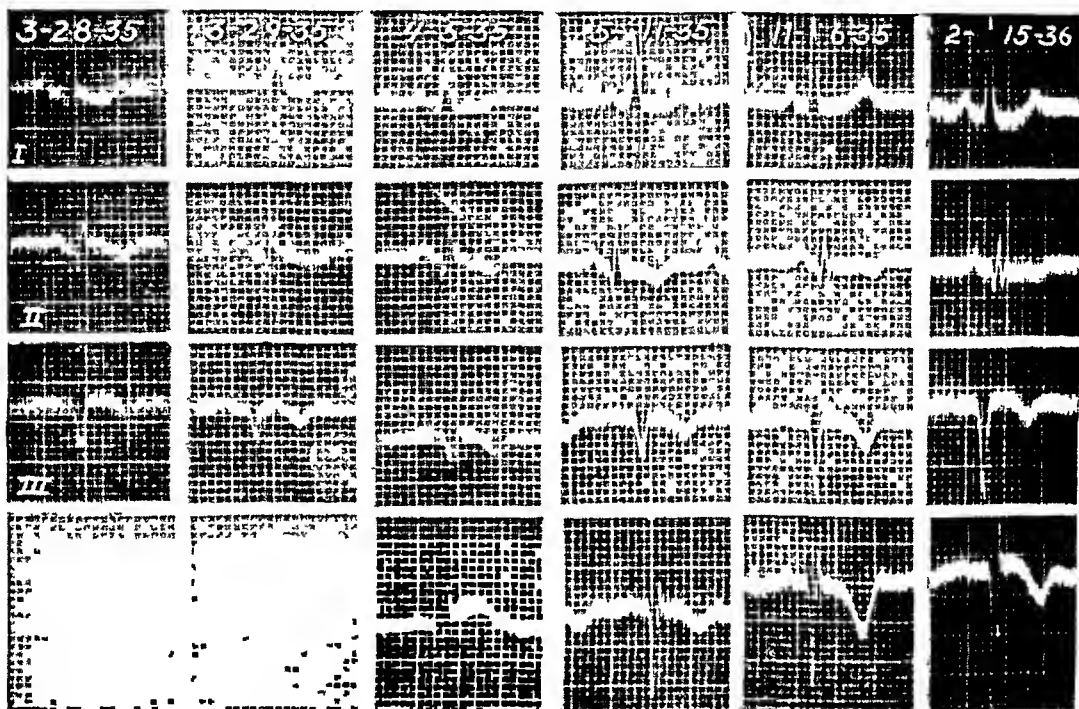


FIG 1 Sections of serial electrocardiograms from patient with acute coronary occlusion complicated by pericardial effusion. The first curve taken three weeks after onset of attack, dated 3-28-35, shows a late Q-T pattern indicating infarction in the posterior basal portion of the left ventricle. No appreciable change is noted in the next curve taken the following day, in spite of fact that 500 c.c. of pericardial fluid had been removed. On 5-11-35 little change is noted in the electrocardiogram, although by this time all clinical signs of pericardial involvement had vanished, indicating the initial alterations were due to coronary occlusion rather than the complicating pericarditis. The curve of 11-6-35, showing some increase in voltage of the ventricular complexes, was taken just prior to resection of carcinoma of the cecum, while the last curve, taken 2-15-36, was after complete recovery from this operation (Lead IV, made with right arm electrode over fourth left interspace, the left leg electrode serving as indifferent electrode).

MR 6.5 cm, ML 10 cm, giving a cardio-thoracic ratio of 55 per cent (Figure 3-A). An *electrocardiogram* on the same date showed no significant change except that in Lead IV, the RS-T segments were no longer elevated and T₄ was now inverted. The patient was permitted gradually to be up and about, and, ten weeks after the onset of his attack, was able to go north where his strength and weight further improved, and roentgenologic reexamination of the colon showed no demonstrable increase in the carcinoma. On his return south the following November there were no physical signs of heart disease, the blood pressure was 135 systolic and 80 diastolic, and the

heart appeared, on fluoroscopy, to be of normal size and contour. An *electrocardiogram* at this time showed improved voltage, T_1 frankly positive and deeper inversion of T_4 .

As his recovery now seemed maximal, laparotomy was performed under spinal anesthesia, by Drs J W Snyder and J C Turner. An adenocarcinoma of the cecum (grade 2) was found without malignant fixation of the parietes, or any glandular, pelvic shelf, or liver involvement demonstrable. Resection of the cecum and part of the ascending colon was followed by a Wetzel enterostomy proximal to an end to side anastomosis. A direct transfusion of 500 cc of blood successfully overcame the moderate shock produced. The post-operative course was noteworthy for its smoothness, there being an average amount of abdominal discomfort, but no circulatory symptoms other than occasional mild precordial pains. The enterostomy wound eventually closed, and the patient was up and about within a few weeks.

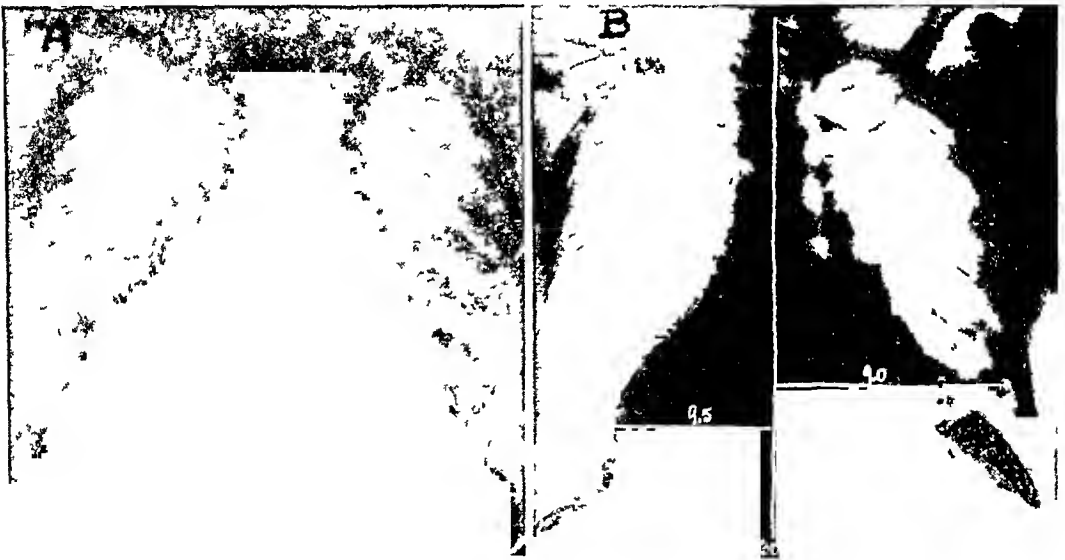


FIG 2 Heart films made with portable equipment. A—taken 3-27-35, patient semi-recumbent, 30 inch distance, 3 weeks after acute coronary thrombosis, showing pericardial effusion. B—taken the following day, 2 hours after withdrawal of 500 cc of pericardial fluid, erect position, 5 ft distance, transverse "cardiac" diameter 18.5 cm, internal chest diameter 30 cm, CT ratio 60 per cent.

A *teleroentgenogram* on February 15, 1936, nearly a year after the acute episode (figure 3-B), disclosed a normal cardio-thoracic ratio of 49.3 per cent (total transverse cardiac diameter 14.8 cm, MR 5.3 cm, internal diameter of the chest 30 cm). An *electrocardiogram* the same day showed little change from the previous record. The patient was last seen in April 1937 and felt very well except for moderate fatigue and occasional vertigo. He had gained 25 pounds (11.3 kg) in weight, and was able to walk two miles a day without discomfort. The *electrocardiogram* at this time showed no further change.

IN REGARD TO ELECTROCARDIOGRAPHIC SIGNS OF PERICARDITIS

The changes in the *electrocardiogram* produced by *uncomplicated pericarditis*, with or without effusion, have been fully described recently by Schwab and Herrman.⁹ Their conclusions, based on a review of the relevant literature

since the observations of Oppenheimer and Mann¹⁰ in 1923, together with their own study of serial electrocardiograms in seven cases of pericardial disease, may be summed up as follows. The usual *early* alterations consist of low voltage of the ventricular complexes and elevation (never depression) of the RS-T segments in Leads I and II or all three conventional leads, although these changes may be lacking. The usual *late* alteration consists of inversion of the T-waves in the same leads, either following the regression of the RS-T segments to the isoelectric level, or appearing without preceding RS-T segment elevation. In the few instances where Lead IV was taken slight deviation in the RS-T segments and positive or biphasic T-waves were revealed. Although mimicking the electrocardiogram following acute coronary occlusion, pericardial disease is differentiated by the *absence* of reciprocal relationship in the RS-T



FIG 3 Teleoroentgenograms of the same patient. A—taken 5 weeks after the paracentesis showing further decrease in “cardiac” size. Transverse “cardiac” diameter 16.5 cm, internal diameter of chest 30 cm, CT ratio 55 per cent. B—taken 7 months after A, and 3 months after resection of the colon. The transverse “cardiac” diameter is 14.8 cm, CT ratio 49.3 per cent or normal.

deviations and T-waves in Leads I and III, and by the *absence* of abnormal Q-waves. Serial electrocardiograms show that as the pericarditis heals the T-waves gradually become positive again.

The typical electrocardiographic pattern in *acute coronary occlusion complicated by pericarditis* is featured, according to a recent study made by Baines,¹¹ by elevation or dome-shaped upward rounding of the RS-T segment in all three conventional leads, without the reciprocal depression of the RS-T segment either in Leads I or III characteristic of myocardial infarction. This change is followed by inversion of the T-wave in all conventional leads, or in some instances by a T-pattern typical of late coronary occlusion. Even early, however, the Q-pattern may be so typically developed that myocardial infarction, and its location, is indicated. In other words, this author holds that if acute coronary occlusion is attended by pericarditis, the characteristic early reciprocal deviation

in the RS-T segments in Lead I and III is overshadowed by the signs of pericarditis, i.e. elevation or dome-shaped upward rounding of the RS-T segments in all three leads, the only intact evidence of infarction in the early stage being the characteristic Q-pattern. There was no clinical evidence of pericardial effusion in the cases comprising Barnes' study.

In the case under discussion, proof that the first electrocardiographic changes were due to acute coronary occlusion (of 21 days' duration) rather than to the pericarditis, rests on the lack of electrocardiographic improvement following the disappearance of the clinical signs of pericarditis. Granting this, the retention of the characteristic late reciprocal relationship of the RS-T segments and T-waves in Leads I and III together with a typical Q_s pattern, suggests that pericarditis even with effusion does not appreciably alter the electrocardiographic pattern induced by acute coronary occlusion if the infarction is in the posterior basal portion of the ventricle.

The electrocardiographic pattern in this case, however, need not be taken to controvert the above conclusions of Barnes¹¹ for of the eight cases studied by that author seven were eventually shown to have anterior or apical infarction in the left ventricle, and the remaining case suggesting posterior basal infarction did not show exactly typical changes in the electrocardiogram, and may have been an instance of combined posterior and anterior infarction of the left ventricle, as pointed out by the author, since no friction rub was heard and autopsy was lacking. It is quite likely in view of the foregoing, that the electrocardiographic pattern noted by Barnes is typical only of anterior or apical infarction in the left ventricle complicated by pericarditis, and it may eventually be shown in additional cases that the characteristic electrocardiographic pattern of infarction of the posterior basal portion of the left ventricle is not overshadowed by the advent of pericarditis.

SUMMARY

A case of acute coronary thrombosis with massive pericardial effusion necessitating paracentesis has been described. This case was further complicated by adeno-carcinoma of the cecum found during convalescence and later resected successfully.

The electrocardiographic signs of pericarditis, including *pericarditis episteno-cardica*, have been briefly reviewed. The study of serial electrocardiograms taken in the present case suggests that when infarction of the posterior basal portion of the left ventricle is complicated by pericarditis, the electrocardiographic signs of this complication will be lacking, in contra-distinction to the electrocardiographic pattern observed when pericarditis follows infarction of the anterior or apical portion of the left ventricle.

Note. When preparing this report I overlooked the article of Wolterth and Wood (Arch Int Med, 1935, 61, 77) in which they showed that electrocardiograms similar to those depicted by Barnes may be due to infarction involving both the anterior and posterior surfaces of the left ventricle.

Recently Vanderveer and Norris (Am Heart J, 1937, 14, 31) have adduced evidence that the electrocardiographic changes in pericarditis are the result of superficial myocarditis associated with the pericarditis.

The patient described in this case report is free from all complaint at present, three years after the onset of his attack. His electrocardiogram shows no change from the last one illustrated.

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HYPERINSULINISM ASSOCIATED WITH HYPOTHYROIDISM TWO CASE REPORTS

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THE following cases are reported because the findings indicate that there may be a cause and effect relationship between hypothyroidism and hyperinsulinism or at least that hypothyroidism may aggravate hyperinsulinism. Considerable experimental work has indicated a definite interrelationship between the secretion of the thyroid and that of the islet portion of the pancreas. It has been shown also clinically, that the injection of insulin changes the basal metabolic rate, but in a review of the literature available to us, no case report has been found indicating a definite relationship between hyperinsulinism and hypothyroidism. Tedstrom,¹ however, reports a case with a hyperinsulinism type of blood sugar curve in which the basal metabolism reading was minus 22. He states that the basal metabolic rate was increased to normal with thyroid extract without relieving any symptoms except that of headaches. He does not indicate, however, that the glucose tolerance test was repeated while the metabolism was at a normal rate.

Marine² reports Falta as believing that the thyroid and pancreas are antagonistic. Falta found that thyroidectomized dogs were less sensitive to the hyperglycemic action of epinephrine than normal animals. This, so Marine states,

* Received for publication May 29, 1937.

has been confirmed by Bodansky and by Burns and Marks. Bodansky reported that thyroidectomized sheep were more sensitive to insulin than normal animals. Marine also is authority for the statement that thyroid or thyroxine fed to thyroidectomized rabbits decreases the hypoglycemic action of insulin.

Simnitzky and Komendantowa³ by rather extensive histological studies on animals found that the continued injection of insulin produces a diminution of the function of the thyroid which manifests itself morphologically in the flattening of the epithelium lining the walls of the acini and in a retention of the colloid in the acini.

Ernst and Kaufman⁴ gave one gram of dextrose per kilogram of body weight to 11 patients suffering from various diseases. They then gave one-fifteenth of a unit of insulin per kilogram of body weight to each patient and recorded blood sugar readings at 20 minute intervals.

After the ingestion of the dextrose and the injection of insulin the average increase of blood sugar reading was as follows: After 20 minutes 34.7, after 40 minutes 45.5, after 60 minutes 44, and after 80 minutes 38.7. The same procedure carried out on a small group of patients suffering from Basedow's disease and from hyperthyroidism gave the following average increases in blood sugar readings: After 20 minutes 41.1, after 40 minutes 51.7, after 60 minutes 54.4, and after 80 minutes 47.6. This clinical experimental work, as will be observed, indicates that increased activity of the thyroid inhibits to some extent the action of insulin so that the blood sugar rises higher after dextrose is given in the hyperthyroid and exophthalmic goiter cases than in those whose thyroid function is less active.

These latter observations are also in accordance with the observations of those clinicians who have noted that in cases of diabetes associated with hyperthyroidism the surgical treatment of the hyperthyroidism lessens the severity of the diabetes. Apparently the removal of an excess of thyroid secretion allows the production of more insulin.

The following cases add further evidence tending to substantiate the observations outlined above and suggest a treatment for some cases of hyperinsulinism other than diet and surgery.

CASE REPORTS

Case 1 E. C. H., white, male, aged 36, a bookkeeper, was admitted to the Birmingham Baptist Hospital on December 25, 1935, and was first seen by me shortly afterward. His wife gave the history that she had been awakened about 3:00 a.m. and had found the patient in a convulsion during which he foamed at the mouth and bit his tongue to the extent that the froth was quite bloody. He was unconscious for about 30 minutes after she awakened, but seemed normal after consciousness returned. He was admitted to the hospital about one-half hour after regaining consciousness.

When I first saw him, a few minutes after his admission, he was rational and comfortable except for a slight headache. He did not recall anything immediately preceding the convulsion. Physical examination revealed a well developed and well nourished young man apparently relaxed and comfortable in bed. He was well oriented. Nothing abnormal on physical examination was found except a swollen and slightly lacerated tongue. Pupils were equal and symmetrical and responded to light. Patellar, biceps and abdominal reflexes were normal. The Babinski sign was not present.

Past history was irrelevant except that he had awakened one morning several weeks before with a sore and swollen tongue. He also stated that he had great difficulty keeping awake at times and had, on one occasion, fallen asleep while driving his car.

His family history was irrelevant except that one sister had diabetes and one niece had exophthalmic goiter.

Routine laboratory examination on admission was negative. A spinal puncture was done some hours after admission. This revealed the spinal fluid under normal pressure. Seven cells were found per cubic millimeter and there was a trace of

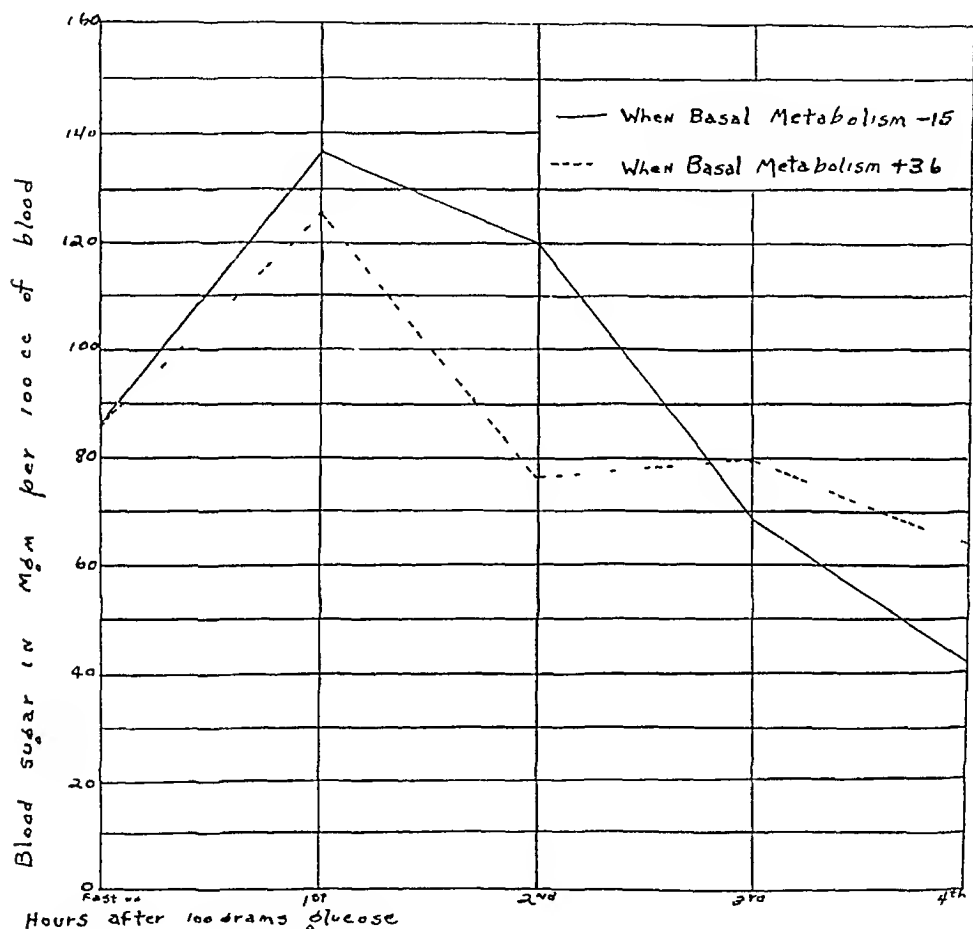


FIG 1 Case 1

globulin. The Wassermann was negative. A fasting blood sugar determination a few hours after his admission was 108 mg per 100 c c of blood.

A few days later a glucose tolerance test was done. After a redetermination of the fasting blood sugar the patient ingested 100 grams of glucose and hourly blood sugar readings were taken for four hours. His fasting blood sugar was 87 mg per 100 c c, after one hour it was 137, after two hours 120, after three hours 68, and after four hours 42, as shown in figure 1. A basal metabolic reading taken immediately before the ingestion of glucose gave on two tests minus 15 each time. The patient was put on three grains of desiccated thyroid gland which he took daily, with

rest intervals, until four and one-half months later. The basal metabolism reading at this time was plus 36. A glucose tolerance test on the following day gave the following results, as shown in figure 1. The fasting blood sugar was 87 mg per 100 c.c., after one hour 127, after two hours 77, after three hours 80, and after four hours 75. This suggests that the increased utilization of thyroid secretion in the body had depressed the production of insulin so that the blood sugar had remained higher and thereby prevented further convulsions. Until this date the patient has had no further convulsions.

Case 2 C. V., white, male, aged 39, locomotive fireman, was seen at the office on June 30, 1936. His chief complaint was of recurring attacks of convulsive seizures which were accompanied by loss of consciousness. The first one had occurred on July 27, 1935. The attacks, he stated, usually started with twitching of the muscles of the right side of the face and a bending of the body over to the right side. They were preceded by cold chills up and down the spine and a feeling of lightness in the head. He had noticed that the attacks had always occurred when he had gone without food for an unusually long time. His friends had told him that the convulsive twitching became generalized over his body and that he would remain unconscious for 10 or 15 minutes. He states that for 20 or so additional minutes he would be disoriented and unable to talk. There had been probably 15 or 20 such attacks before the consultation on June 30, 1936. The last one had occurred five days previous to his visit to the office. He stated that in addition to those attacks he had had a rather marked loss of memory for recent events. Past history and family history were irrelevant except that his father had been excessively overweight.

Physical examination at this time revealed a well developed and overweight white male, 66½ inches in height and weighing 234 pounds. Nothing else abnormal was found on physical examination. The laboratory examination including a fasting blood sugar was normal except that the basal metabolism reading was minus 20. A glucose tolerance test, however, gave the following results: Fasting blood sugar 85 mg per cent, first hour after 100 grams of glucose 128, second hour 112, third hour 55, and fourth hour 56 mg per 100 c.c. of blood. It will be noted that a low of 55 mg per 100 c.c. of blood occurred three hours after the ingestion of the glucose.

Experience with the previous case caused us to try to control the hyperinsulinism by increasing the metabolic reading to normal with thyroid extract. Accordingly we put this patient on four grains of thyroid daily. On July 23 the basal metabolism reading was minus 38. At this time the glucose tolerance test was repeated with results as follows, as shown in figure 2: Fasting blood sugar 92, first hour after glucose 174, second hour 124, third hour 84, fourth hour 80, fifth hour 88, and sixth hour 92 mg per 100 c.c. of blood. The patient had continued to have occasional attacks so we increased the thyroid dosage to 5 grains daily and on August 12, about three weeks later, we repeated the basal metabolism reading and the glucose tolerance test. The basal metabolism reading was plus 75 and the glucose tolerance test was as follows (figure 2): Fasting blood sugar 92, first hour after glucose 184, second hour 141, third hour 95, fourth hour 65, fifth hour 78, and sixth hour 90 mg per 100 c.c. of blood.

In spite of this change in glucose tolerance the patient reported that he was having still occasional attacks of the same type of convulsive seizure. They were, however, not so numerous and he felt much better than he had felt previously.

We had allowed him to manage his diet as he chose. We inquired of him what his diet was and he explained that he had been visiting with friends and relatives and eating a great deal of pies and cakes and other carbohydrates. We felt, however, now that we would not be able entirely to control the attacks with thyroid extract. We therefore placed him on a high fat and low carbohydrate diet, as has been sug-

gested by Harris⁵ This he has followed now for about two and one-half months with only one such attack We obtained the history in regard to this attack that he had eaten a heavy meal one evening and had taken a purgative that evening and the morning after The attack occurred at the noonday meal the day following the indiscretion in diet A further follow-up on this case indicates that he still has an occasional attack

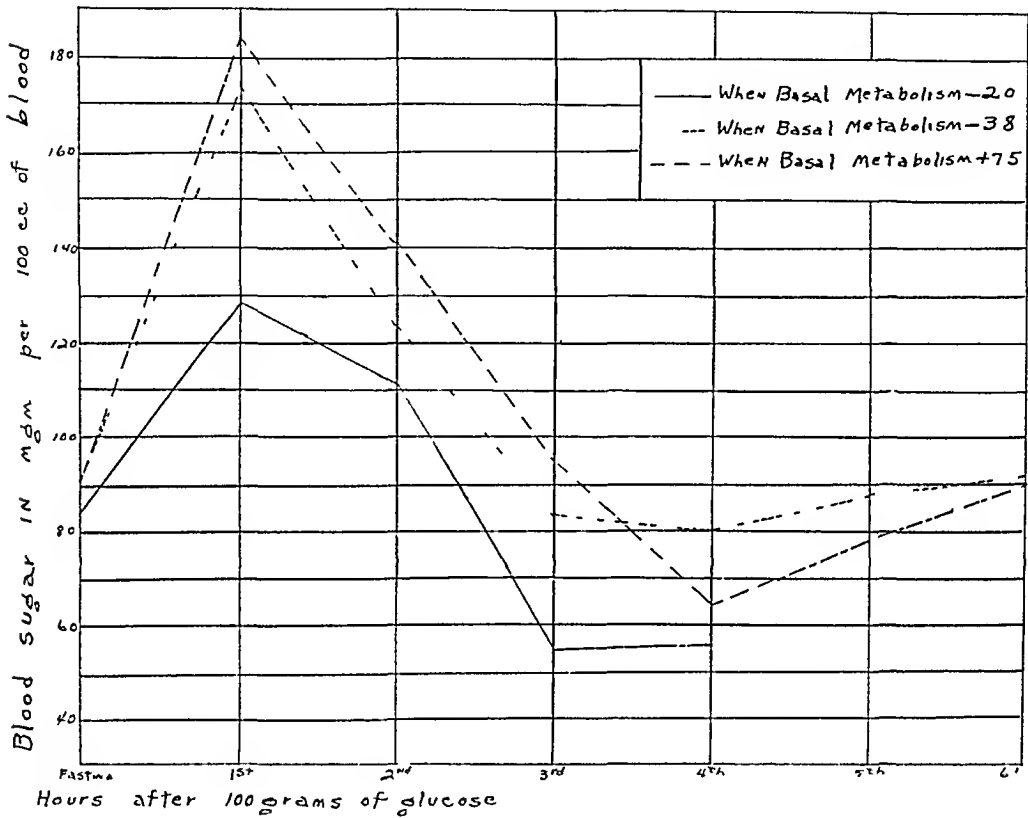


FIG 2 Case 2

SUMMARY

1 The literature is briefly reviewed and an indication of mutual antagonism between the thyroid and islet secretions is noted No attempt is made to determine whether the antagonism is direct or through the intermediary of some gland such as the pituitary

2 Case reports of hyperinsulinism associated with hypothyroidism are given

3 The effect on the hyperinsulinism curve of the feeding of desiccated thyroid is noted Further progress of the cases under thyroid medication is given This follow-up indicates that some cases of hyperinsulinism may be improved if not held entirely in check by the use of desiccated thyroid gland It is realized, however, that results of such treatment in a large number of cases followed over a much longer period of time would be necessary before any trustworthy conclusions could be drawn

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MUSCULO-SPIRAL PARALYSIS AFTER SERUM INJECTION (RECURRING AFTER SECOND INJECTION)

By LEOPOLD BRAHDY, *New York, N Y*

L D, a hospital orderly 25 years of age, was using alcohol in excess. He had never been in any occupation which could have exposed him to lead. On February 24, 1934, he was given 1500 units of tetanus anti-toxin because of a laceration of the sole of the foot. One week later, he complained of severe pain in the neck and in both arms. Examination showed the muscles of the arms tender and in some degree of spasm. The diagnosis of polyneuritis was made. On April 3, examination showed left wrist drop, no anesthesia. The wrist drop persisted several months and finally disappeared, leaving no residual signs or symptoms. In August 1934, he was admitted to the hospital for two days for acute alcoholism. No abnormality of the extremities was noted at that time.

In 1934, he had a lobar pneumonia. No serum was used and he made an uneventful recovery.

On August 22, 1935 he was pinched over the dorsum of the elbow by a patient suffering from cerebro-spinal meningitis. There was no open wound. However, another orderly (J G) had been scratched by this same patient several days before and had developed gas bacillus infection from the scratch. This fact frightened L D and he requested and was given "1500 units of tetanus anti-toxin and a prophylactic dose of gas gangrene bacillus" serum. This injection was given subcutaneously in the left upper arm. He is quite certain that there was no intramuscular injection. He had no symptoms until eight hours later when he developed pains in the left arm radiating from the spine to the fingers. Two days later, he noticed left wrist drop. There was no urticaria nor any other anaphylactic symptoms. Physiotherapy treatments were administered for several months, but the wrist drop persisted.

Since the patient is well acquainted with medical procedures, his statement that the injection was subcutaneous is more reliable than would be that of another layman. In spite of that history, we considered the possibility of direct nerve injury. The absence of any pain, weakness or numbness, however, until eight hours after injury, was entirely inconsistent with this hypothesis.

In November 1935, he was readmitted for three days for acute alcoholism.

* Received for publication May 13, 1937

Twenty months after the onset of the second wrist drop, examination by Dr Byron T Stookey at the Neurological Institute was reported in part, as follows

"The neurological examination is entirely negative except for the presence of rather lively but equal reflexes of both lower extremities and the right upper. The left upper reflexes, supplied by the seventh cervical, namely, the triceps and the ulnar, are diminished. The ulnar jerk is absent on the left side and is present on the right. There is definite atrophy of the extensors of the fingers of the left hand. The *supinator longus* contracts, as does also the *brachia radialis longus* and *brevis*, but there is no extension of the fingers or of the thumb. In short, this patient has evidence of a wrist drop which has in part recovered sufficiently to permit part extension of the wrist but no recovery has taken place in the extensors of the fingers or the thumb."

In 1932, Wilson and Hadden¹ reviewed cases of peripheral nerve lesions after serum injection, and in 1933 Wulf² reported nerve lesions after serum injection. There is no case reported of transient paralysis with recurrence of the paralysis in the same nerve after a second injection. We have here a case of paralysis (now permanent) recurring after a second injection. Excessive alcoholism may have rendered the peripheral nerves susceptible. Although I have seen many hundreds of patients who had prophylactic or therapeutic serum injections, this is the only one resulting in any permanent defect. I believe that we may accept Wulf's statement to the effect that disturbance of the nervous system is so rare that it does not limit the indications for the use of serum.

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EDITORIAL

THE PRESIDENTIAL ADDRESS

THE Presidential address of Dr James Howard Means at the Convocation of the College attracted unusual attention. The membership of the College will have the opportunity of reading the full text of this able speech in the May issue of the *ANNALS*. However, because of the misinterpretation of certain of Dr Means' remarks it has seemed advisable to the Regents that in this issue there should appear a statement addressed to the membership of the College and to the general medical profession.

In some quarters it was apparently thought that Dr Means had called upon the medical profession to revolt against the leadership of the American Medical Association. Indeed, it was suggested that under certain conditions the College should take away from the American Medical Association the function of representing the medical profession. Naturally 'such statements have not failed to be disturbing to those of our Fellows who did not hear Dr Means' address.

In his remarks Dr Means was critical of the recent policy of the American Medical Association which he summarized as standpatism. He expressed himself as believing that since the organization of the American Medical Association is that of a democracy it would be in a healthier state if it always contained, in addition to the existing administration, an effective opposition party so that there might be active discussion of vital issues. He felt that it was desirable that those who believe in popular government should bestir themselves to bring this about.

It is no more a revolt against the American Medical Association to criticize its present policy and to suggest that within its membership an effective opposition should be organized, than it is revolt against the United States for one of its citizens to criticize the New Deal and to express a fervent wish for a successful opposition party.

Dr Means made it very plain that he was not giving voice to a policy, nor to a political program of the College, for in his analysis of the purpose of a college of physicians he stated his opinion as follows: "I have said what I have said in order to indicate what I conceive to be the fundamental difference between a college of physicians and a national or state medical society. Each has its use but they are different. The college is not in competition with the medical association. The college should be a counterpart of the university, not that of the state. It should be as unthinkable for us to have a College policy regarding social, economic, political or scientific aspects of medicine as for one of our universities to take sides in a political campaign. It should also be unthinkable that we should at any time be unwilling to hear all sides of any problem related to the practice of medicine."

It is evident therefore that Dr Means, believing as he does that the College should be a body without a policy, was expressing only personal views concerning the advisability of an opposition party in the American Medical Association, and least of all was he presaging a future supplanting of the Association by the College

The interpretations to which we have referred are therefore quite unwarranted by the content of Dr Means' speech

Because of the questions raised by this incident the following account of the position taken by the Officers and Regents of the College in the past may be of interest

Among the Objects of the College mentioned in the Constitution (Article III, Sec 1a) is that of "maintaining and advancing the highest possible standards in medical education, medical practice and clinical research" Since the Officers and Regents are empowered to represent and to act for the College in matters defined in the Constitution and the By-Laws the above section would permit the Officers and Regents by formal motion recorded in their minutes to commit the College to any policy or action which in their opinion would further these objects However, up to this time the conception of the proper rôle for the College has been in accord with Dr Means' definition The College has not felt that it should have any policy other than that of the ethical principles embodied in its Fellowship Pledge It has so far followed a precedent of holding aloof from any official action, or pronouncement of opinion bearing upon disputed questions of medical practice It has become customary to refer inquiries, requests for opinions, etc on such matters to the Committee on Public Relations who submit a report to the Board of Regents The Board of Regents has up to this time consistently stated that the College was not committed to any policy and that its function was not that of serving as an arbiter It seems highly probable that this precedent will continue in force It seems certain, moreover, that should some future emergency in the affairs of the medical profession induce the Officers and the Regents of the College to attempt to marshall the strength of its membership in defense of some vital principle, a first step, before pronouncing a College policy in any contentious question, would be to submit the proposal to the vote of the Fellows of the College in a General Meeting

The College has been and is unreservedly devoted to the principle of free speech The more vital and the more controversial a topic is, the more important it is that the members of the College should hear the best obtainable presentation of both sides The College will keep its meetings open to the expression of any sincere opinion upon any side of any medical problem Nor does the College intend to taboo any subject from discussion by its own Fellows, Masters, Governors, Regents or Officers

It should be plain to the membership, however, that no statement by any one of these constitutes a College policy

REVIEWS

Arteriovenous Aneurysm By EMILIE HOLMAN, M D 244 pages, 15 × 22 cm The Macmillan Co, New York 1937 Price, \$5 00

This recent book by Holman justly deserved the recognition given when it was awarded the Samuel D Gross prize by the Philadelphia Academy of Surgeons. The first part of the book deals with experimental work and if studied carefully yields clearer understanding of the physiological adjustments to the presence of arteriovenous fistulae. The author then discusses in detail both congenital and acquired arteriovenous fistulae and aneurysms of the extremities and other parts of the body. This portion of the book is a most excellent summary of recent clinical investigations of these conditions.

The book on the whole is a splendid piece of work from the experimental, clinical and historical points of view. It will prove to be of value to the teacher, both of medicine and of surgery, and especially to the research worker in this field.

T B A

Radiation Therapy By IRA I KAPLAN 558 pages, 16 × 24 cm Oxford University Press, New York 1937 Price, \$10 00

This volume will be of interest to the internists as well as to those treating disease by means of radium and roentgen-rays. It is written from a practical viewpoint. Dr Kaplan's wide experience in radiation therapy is evident in every chapter. The chapter on physics by Braestrup is unusually clear so as to be readily understandable to any physician. The illustrations are excellent and the extensive bibliography will be helpful to students. The subject cannot be fully covered in one volume and certain chapters, notably those on radiation therapy in neurological disease, inflammatory processes and bone diseases, seem too brief to be adequate. It can be recommended as an excellent reference on radiotherapy.

W L K

Medical Greek and Latin at a Glance By WALTER R AGARD Second edition revised 87 pages, 16 × 25 cm Paul B Hoeber, Inc, New York 1937 Price, \$1 50

This little volume will prove of real help in understanding many of the terms in our bilingual medical nomenclature. It is really a glossary and makes plain the derivation and meaning of many words to those who have little Latin and less Greek. It meets a real need.

L A M K

Essentials of Psychiatry By GEORGE W HENRY, M D, Associate Professor of Psychiatry, Cornell University Medical College, New York City 465 pages, 15 × 24 cm The Williams and Wilkins Company, Baltimore 1938 Price, \$5 00

This is the third edition of a very well known book, which has gained popularity because it presents the essentials of psychiatry in understandable language. This specialty has made rapid progress, and Dr Henry has brought his book up to date.

In his twenty chapters the author has steadfastly held to his conclusion that psychiatry is as scientific as any other branch of medicine, and that in its practice it is necessary for the physician to take all of the facts regarding illness into consideration. "There is no short road to the understanding of human reactions and it is

only after years of training and experience that the physician is prepared to deal adequately with personality disorders"

The first ten chapters discuss the development of the personality and its disorders. Dr. Henry clearly describes the various types of psychopathology, discussing each classification in the following order: definition, frequency, causes, symptoms, types, course of illness, prognosis, excerpts from illustrative cases, and discussion of the classification.

The last ten chapters take up method and purpose of mental examination, principles of treatment, psychiatric nursing, psychopathology of the normal, mental hygiene, disorders of childhood, psychiatric social service, medico-legal aspects, psychiatric history, and milestones in psychiatric history.

J. L. McC

Practical Talks on Kidney Disease By EDWARD WEISS, M.D., Professor of Clinical Medicine, Temple University School of Medicine. 176 pages. 14.5 × 22 cm. Charles C. Thomas, Springfield and Baltimore. 1937. Price, \$3.00.

This small volume makes no pretensions to being an exhaustive treatise on the subject of renal disease. The title is well chosen. Nevertheless, it contains the essential information presented in a readable fashion. There are brief chapters on the physiology of the kidney, impairment of renal function, and tests of renal function. The author then presents the principal signs and symptoms of renal disease and devotes short chapters to the more important ones such as edema, albuminuria, hypertension, retinal lesions (illustrated), etc. The various clinical syndromes and their treatment are then described. Part VII deals with hypertension and the rôle it may play in kidney disease.

Those who have made a particular study of this field probably will gain nothing new from this book. The reviewer recommends it to practitioners and students.

W. S. L., Jr.

Physical Diagnosis By RALPH MAJOR, M.D., Professor of Medicine in the University of Kansas. 457 pages, 15.5 × 24 cm. W. B. Saunders Co., Philadelphia. 1937. Price, \$5.00.

This textbook is a comprehensive survey of physical diagnosis. It includes chapters on all parts and all systems of the body, with two additional, one on pain and the other on history taking.

Dr. Major includes so much information, with so many interesting and important little details, that the result is at times confusing. This is obviated to a certain extent by the splendid illustrations, both photographs and diagrams which help to elucidate the text.

Those interested in Dr. Major's former book, "Classic Descriptions of Disease," will be pleased to know that the subject is approached as much as is possible from an historical point of view. Besides the introductory chapter, with its accounts of some of the great personages in medicine, the text includes many original descriptions of disease and some original illustrations.

The clinical side of physical diagnosis is stressed, but one wishes that a little more space had been given to those chapters dealing with diseases of the heart and lungs. The chapter on the pulse, however, is excellent and, but for the omission of any mention of auricular flutter, might serve as a standard for instructors in physical diagnosis.

The usefulness of the book is enhanced by the splendid bibliographies that the author has appended to each chapter.

R. A. R.

Alcohol One Man's Meat By EDWARD A. STRECKER, M.D., and FRANCIS T. CHAMBERS, JR., M.D. 230 pages, 14 × 21 cm Macmillan Co., New York 1938 Price, \$2.50

This volume dealing with "Another Man's Poison" constitutes an excellent graduate course on how to handle chronic alcoholics. From cover to cover it is packed with interesting information concerning the physiology and toxicology of alcohol, the psychology and pseudo-philosophy of the alcoholic patient and the ways and means for the intensive psychical reeducation of the victim of alcoholism. No thinking physician can read it without deepening his understanding of the problems of alcoholism and increasing his ability to cope with them, for the treatment suggested is directed not so much to the disease itself as to its underlying causes.

The authors question the stimulating action of alcohol and regard its effect rather as that of a camouflaged narcotic, the deception of stimulation arising from the release of the lower nerve centers from the control of the higher by its narcotizing power. Alcohol is used commonly by the laity because it is the only narcotic that can be purchased inexpensively in a glass or bottle and without a doctor's prescription. It is used as a salve to the ego as, in the beginning at least, it acts magically in soothing the painful wounds of personal belittlements and feelings of insignificance.

The authors differentiate normal from abnormal drinkers. The normal drinker uses alcohol in moderate amounts as a socially accepted gesture and for purposes of conviviality and rarely gets into trouble from it. Through its use the adult attains temporarily a childlike state of mind and freedom from the behaviorism demanded by maturity. Such a one drinks to exaggerate reality because he finds reality enjoyable. The border line between normal and abnormal drinking is crossed when alcohol is used as an aid in the adjustment to reality. The abnormal drinker is the individual who cannot face reality without alcohol, but whose adequate adjustment to reality is impossible as long as he uses alcohol. In other words the abnormal drinker is an abnormal individual seeking release from reality through the medium of alcohol. Treatment of alcoholism therefore involves the management of an abnormal personality. The authors take their cues for treatment from the psychotherapists who have led their neurotic patients suffering from neurasthenia, anxiety states, hysteria or compulsive neuroses back to the normal planes of life. Many of the procedures used in these various disturbed psychical states are equally effective in the management of the chronic alcoholic.

The authors believe that the psychoneurosis which is responsible for much of our alcoholism must be traced back to its causes and these must be met by appropriate psychotherapy. The underlying neuroses are due most frequently to unfavorable early home life, constitutional predisposition, or to chronic disease, sex conflicts, financial difficulties, restricted outlets or actual mental defects.

According to the authors, treatment should not be started while the patient is still drinking, in fact not until the patient sees his own need, seeks help on his own initiative without outside persuasion or coercion, and is willing and eager to participate in his own cure. The psychotherapist should not undertake treatment until he is convinced that it is possible to bring about a state of mind in his patient that desires not to drink any more. The patient must understand in the beginning that it is impossible for him ever to learn to drink in moderation. He must be willing to face life without alcohol. The treatment advised, consists of prescribed rules and schedules, psychological treatments, mental reeducation and physical adjustments. The patient must be carried from lower to higher and mature levels, must be taught his own needs, gain an insight into his crippled condition and taught how to help to cure himself. He must practice abstinence throughout the period of management. The treatment usually necessitates at least one year of supervision and in all about one hundred conferences with the psychotherapist.

The reviewer believes that this book constitutes a real contribution to medicine. The treatment as outlined seems ideal for the more intelligent and tractable alcoholics, especially if enthusiastically applied by a properly qualified psychotherapist. Whether or not this or any other system of treatment will meet the needs of the average and less intelligent drunkard is open to question. Certainly it would not appear to be more costly or time consuming than present methods of management which entail long or frequent and intermittent hospitalization.

L G R

COLLEGE NEWS NOTES

GIFTS TO THE COLLEGE LIBRARY

Grateful acknowledgment is made of the receipt of the following donations to the College Library of publications by members

Books

Dr John S Chambers (Fellow), Lexington, Ky—"The Conquest of Cholera",
The American Foundation Studies in Government—Volumes I and II, "American
Medicine Expert Testimony Out of Court"

Reprints

Dr Alonzo F Brand (Fellow), Fayetteville, N Y—one reprint,
Dr Charles H Cocke (Fellow), Asheville, N C—seventeen reprints,
Dr A R Foss (Fellow), Missoula, Mont—one reprint,
Col S W French (Fellow), M C U S Army—one reprint,
Dr P A Gray (Fellow), Santa Barbara, Calif—one reprint,
Dr Edgar F Kiser (Fellow), Indianapolis, Ind—five reprints,
Dr Abel Levitt (Fellow), Buffalo, N Y—one reprint,
Dr C F Morsman (Fellow), Hot Springs, S D—two reprints,
Dr Oliver T Osborne (Fellow), New Haven, Conn—one reprint,
Dr Aaron E Parsonnet (Fellow), Newark, N J—one reprint,
Dr Lee Roy Woodward (Fellow), Mason City, Iowa—one reprint,
Dr Paul A Draper (Associate), Colorado Springs, Colo—two reprints,
Dr Arthur O Hecker (Associate), Polk, Pa—three reprints,
Dr David W Kramer (Associate), Philadelphia, Pa—ten reprints,
Dr Charles E Lyght (Associate), Northfield, Minn—one reprint,
Dr Matthew Molitch (Associate), Philadelphia, Pa—twenty-nine reprints,
Dr Eugene S Sugg (Associate), New York, N Y—one reprint

REGIONAL MEETING OF KANSAS MEMBERS

Members of the American College of Physicians resident in the State of Kansas held their annual meeting and dinner in Wichita, under the Governorship of Dr Thomas T Holt, February 22, 1938 The following program was rendered

- "Treatment of Cardiacs with Oscillator Bed," Dr Harold H Jones (Fellow),
Winfield, Kan ,
- "Medical Problems in Mineral Metabolism," Dr Frances Helen Schiltz (Fellow),
Wichita, Kan ,
- "Peptic Ulcer, Carcinoma Question," Dr H N Tihen (Fellow), Wichita, Kan ,
- "Use of Insulin in Mental Disease," Dr D V Conwell (Associate), Halstead, Kan ,
- "Insulin in Treatment of Schizophrenia," Dr R M Fellows (Fellow), Osawatomie,
Kan ,
- "Cerebral Spinal Pressure Relative to Blood and Circulatory Disturbance," Dr
Thomas T Holt (Fellow and Governor for the State of Kansas), Wichita, Kan ,
- "Simmond's Disease (Pituitary Cachexia)," Dr G F Corrigan (Associate)
Wichita, Kan ,
- "Clinical Phases of Recent Developments in Connection with the More Modern De-
velopments in Cancer Etiology," Dr P M Krall (Associate), Kansas City
Kan

Dr E J G Beardsley (Fellow and Governor for Eastern Pennsylvania), Philadelphia, Pa, spoke on "Medical Conditions Which Simulate Abdominal Emergencies" at the University of North Carolina's Postgraduate Seminar, held at High Point, N C, March 17, 1938

Dr Beardsley also held a morning and afternoon medical clinic at the Sacred Heart Hospital, Allentown, Pa, on March 24 1938

Dr Claude Ellis Forkner (Fellow), who has just completed a five-year appointment as Associate Professor of Medicine in the Peking Union Medical College, has returned to New York and has been appointed Assistant Professor of Clinical Medicine at Cornell Medical School Dr Forkner has also been appointed Assistant Attending Physician at the New York Hospital, and has opened an office for the practice of Internal Medicine and Hematology at 121 East 60th Street, New York, N Y

Dr Paul H Ringer (Fellow), Asheville, N C, has been made President of the Southern Tuberculosis Conference

Dr Charles S Holbrook (Fellow), New Orleans, La, has been made President-Elect of the Southern Psychiatric Association

Dr Paul D White (Fellow), Boston, Mass, addressed the North Side Branch of the Chicago Medical Society, recently, on "Nature, Diagnosis and Treatment of Heart Disease"

The second annual New Orleans Graduate Medical Assembly was held in New Orleans, March 7 to 10 Fellows of the College who participated on the program were Dr Reginald Fitz, Boston and Dr Udo J Wile, Ann Arbor Mich

The tenth annual spring clinical conference of the Dallas Southern Clinical Society was held at Dallas, Tex, March 14 to 17 Guest speakers and their subjects were Dr Russell L Haden (Fellow), Cleveland, Ohio, "Treatment of Arthritis," and Dr Howard T Karsner (Fellow), Cleveland, Ohio, "Research on Hypertension"

Dr Walter P Gardner (Fellow), Hastings, Minn, has been made Superintendent of the Anoka State Hospital

Dr Wallace M Yater (Fellow and Governor for the District of Columbia), Professor of Medicine, Georgetown University School of Medicine, Washington, D C, delivered the annual Kober Lecture at the University March 28 His subject was "Goiter and the Heart An Exposition of the Present Status of Our Knowledge of the Subject, Including Original Research Work in This Field"

Dr Carl J Wiggers (Fellow), Cleveland, Ohio, spoke on "The Dynamics of Hypertension" before the annual meeting of the Federation of American Societies for Experimental Biology, held at the Lord Baltimore Hotel, Baltimore, Md, March 30 to April 2

Dr Felix J Underwood (Fellow), Jackson, Miss, has been appointed a member of the Rockefeller Foundation Board to serve for a period of three years This Board is composed of six members and decides the policy of the Foundation throughout the world

Recent changes at the University of Colorado School of Medicine, Denver, include the following

Dr Philip Work (Fellow), to Professor of Neurology and head of the department, Dr Constantine F Kemper (Fellow), Associate Professor of Medicine, Dr Harry Gauss (Fellow), Assistant Professor of Medicine

Dr Rollin H Stevens (Fellow), Detroit, was guest of honor at a dinner January 28 given by the staff of Grace Hospital, the Detroit Roentgen Ray and Radium Society and the Detroit Dermatological Society, in observance of his seventieth birthday. Among other gifts Dr Stevens received a leather bound copy of the January issue of "Radiology," which was dedicated to him. Each guest received a reprint of the opening article in the journal, entitled "Rollin Howard Stevens, An Anniversary Chronicle of His Useful Life," by Dr Percy Brown (Fellow), of Boston

Dr George R Minot (Fellow), Boston, delivered a lecture January 20 at the Mayo Clinic, Rochester, Minn, on "Some Aspects of the Etiology, Diagnosis and Treatment of Anemia"

Dr Eugene M Landis (Fellow), Assistant Professor of Medicine, University of Pennsylvania School of Medicine, Philadelphia, delivered the annual N W Jones Lectures at the University of Oregon Medical School, Portland, February 9 to 10. Dr Landis spoke on "Capillary Pressure, Capillary Permeability and the Movement of Fluid Through the Capillary Wall" and "The Effects of Pressor Drugs and Kidney Extracts on Blood Pressure and Peripheral Blood Flow"

The Neuropsychiatric Society of Virginia held its first meeting for 1938 at the University Hospital on January 26. Papers were presented by Dr D C Wilson (Fellow) and Dr Dudley C Smith (Fellow), University, Va

At the February meeting of the New York Polyclinic Medical School and Hospital Clinical Society, Dr Lea A Riely (Fellow and Governor for the State of Oklahoma) spoke on "Modern Concepts of Addisonian or Macrocytic Anemia"

Dr Albert Soiland (Fellow), Los Angeles, has been recently elected National President of the United States Naval Reserve Officers Association. Dr Soiland is a Trustee of the Pan-American Medical Association and attended the 7th Congress Cruise during the course of which he contributed three papers to the program

Dr Joseph H Barach (Fellow), Pittsburgh, Pa, addressed the Allegheny-Garrett County Medical Societies at Cumberland, Maryland, on February 25 1938. His subject was "Science of Nutrition and the Treatment of Diabetes"

Dr Walter A Bastedo (Fellow) addressed the Wayne County Medical Society in Detroit, Mich, on March 7, on "Therapeutics and the Physician's Prescription". He has been the recipient of the "Diploma de Honor" of Venezuela Farmaceutica, which governs the standards of drugs in Venezuela

Dr Erwin E Mayer (Fellow) Baltimore, Maryland, addressed the "Association of Dental Surgeons" on March 23, 1938, on "Oral Infections from the Internist's Viewpoint"

OBITUARIES

DR THOMAS BARNES FUTCHER

Thomas Barnes Futcher (Fellow) was born January 1, 1871, in St Thomas, Ontario, Canada, and died February 25, 1938, in Baltimore, Maryland. His early years were spent at home attending the local schools and at the age of 19 he entered the University of Toronto where in 1893 he received the degree of Bachelor of Medicine with high honors. After a year as house officer in the Toronto General Hospital, he went to Johns Hopkins to be a member of the House Staff under his fellow Canadian, Dr William Osler. Seven years were spent in the Hospital, the last three as Resident Physician on the Medical Service. He then entered consultation practice in Baltimore opening an office next door to the home of his beloved chief, Dr Osler. In 1909 he married Gwendolyn Marjory Howard of Toronto who was a daughter of the famous Canadian, Dr Robert Palmer Howard, to whom Dr Osler owed so much of his early medical inspiration.

Dr Futcher's career was one of steady progress in the practice and teaching of medicine. At the time of his death, he was Visiting Physician to the Johns Hopkins Hospital where he was Chairman of the Private Ward Medical Service. He was also Associate Professor of Medicine which is one of the highest academic positions open to part-time teachers at the Johns Hopkins Medical School.

He belonged to many medical societies and in 1931-32 was President of the Association of American Physicians. He was made an Associate of the American College of Physicians in 1925 and became a Fellow in 1930. His interest in the local medical societies was always encouraging, he attended the meetings faithfully, and he was Chairman of the Historical Section of the Baltimore City Medical Society in 1937-38. He was one of the original members of the Interurban Clinical Club and rarely missed the meetings of this Club in other cities.

His medical writings were mostly concerned with metabolic subjects although of his many publications more than half were on such various subjects as haemochromatosis, cancer of the pancreas, erythremia, and disturbances of pituitary function. In Osler's System of Medicine he contributed the sections on Diabetes Mellitus, Diabetes Insipidus and Gout.

Dr Futcher was a member of a distinguished group of American physicians who continued what Osler began, to balance skillful bed-side observation with the newest laboratory method. He taught, by precept, meticulous care in clinical examination but above all he taught, by example, loyalty to the best medical tradition. His friendship was unfailingly kind—no one can remember his saying anything derogatory about a colleague—and the influence of his quiet, genuinely courteous presence will long be felt.

HENRY M. THOMAS, JR.,
Governor for Maryland

DR MICHAEL ANTHONY BURNS

Michael Anthony Burns (Fellow) was born in Philadelphia on May 23, 1884, the son of James M and Mary A (Rowen) Burns. After his early education in the parochial schools of Philadelphia and at St Joseph's College, he entered the Jefferson Medical College from which institution he graduated in 1907.

On the day Dr Burns began the practice of medicine, following his internship, he entered the neurological service of Dr Francis X Dercum, then Professor of Neurology at the Jefferson Medical College. For thirty years, until the beginning of his final illness, he continued in this department in advancing grades as a teacher and, in 1934, his faithful and skilled services were rewarded by election, after the death of Professor Dercum, to the Professorship of Neurology.

During the World War, Dr Burns was neuropsychiatrist to Base Hospital No 38 (The Jefferson Medical College Hospital Unit) and, after the Armistice, he was appointed consulting Neuropsychiatrist to the District of Paris. Dr Burns, at the time of his death, in addition to his teaching and clinical work at the Jefferson Hospital, was Visiting Neurologist to the Philadelphia General Hospital, Neuropsychiatrist to St Mary's Hospital, Consulting Neurologist to the Wills Eye Hospital, St Joseph's Hospital and the Shriners' Hospital for Crippled Children.

He was a Fellow of the American College of Physicians and the Philadelphia College of Physicians, a member of the American Neurological and Psychiatric Associations and of the Philadelphia Neurological and Psychiatric Societies.

Dr Burns was the author of numerous articles on neuropsychiatric subjects and was a frequent contributor to journals specializing upon such presentations.

On October 11, 1910, Dr Burns married Margaret Agnes Keenan of Philadelphia who, with two sons, Paul V and John A, survive him.

Dr Burns was a popular and appreciated physician and his patients will not find it easy to discover another friend and medical counsellor possessing the same happy combination of pleasing and helpful characteristics. Dr Burns loved life and understood people. In common with all truly successful physicians, he thoroughly enjoyed his professional duties. He worked hard, too hard perhaps, to be able to live long.

Dr Burns' death on March 7, 1938, due to coronary thrombosis, was a grievous loss to his family and numerous devoted friends and to the medical profession of Philadelphia.

E J G BEARDSLEY, M D, F A C P,
Governor for Eastern Pennsylvania

ADMIRAL CARY TRAVERS GRAYSON

Admiral Cary Travers Grayson (Associate) was born at Salubria in Culpepper County, Virginia, in 1878 and died in Washington, D C, on February 15, 1938

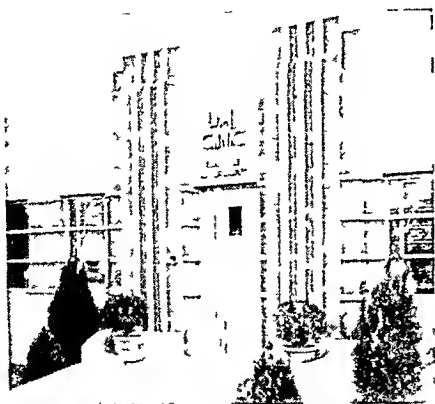
He was educated at William and Mary College (1895-1898) and at the University of The South at Sewanee, Tennessee, where he received his M D degree in 1902 He held a degree from the Medical College of Virginia and graduated from the United States Naval Medical School in 1904 He entered the Navy as an Acting Assistant Surgeon in 1903, and was made a Medical Director with the rank of Rear Admiral on August 29, 1916 He was retired from the Navy December 30, 1928 During these years his professional services were eminent and outstanding He served as personal physician to three presidents, William Howard Taft, Theodore Roosevelt and Woodrow Wilson He had a combination of knowledge, insight and sympathy which are the necessary attributes of the good physician His accomplishments from 1928 until the time of his death are a part of our country's history

Admiral Grayson was a member of the Medical Society of the District of Columbia since January 26, 1916, and an Associate of the American College of Physicians from the inception of the College

In the death of Admiral Grayson America lost one of her most distinguished citizens He had devoted most of his life to doing things for other people The sudden shock of his passing has left sorrow among his many friends and admirers the world over During his life he inspired friendships such as are granted to few men Those of us privileged to know him—and the number was legion—can testify to his gallantry and unbounded loyalty His friends and associates found in him a man in whose personal integrity they could always depend and one in whom trust was never misplaced He had a keen analytical mind which inspired many to seek his rare good judgment At the sick bed and in the council chamber his wisdom was particularly manifest and his logical decisions and timely advice were most helpful to his colleagues His kindly disposition and his unfailing sense of humor saved many a trying situation He was a gentleman in every sense of the word and his host of friends have suffered an irreparable loss

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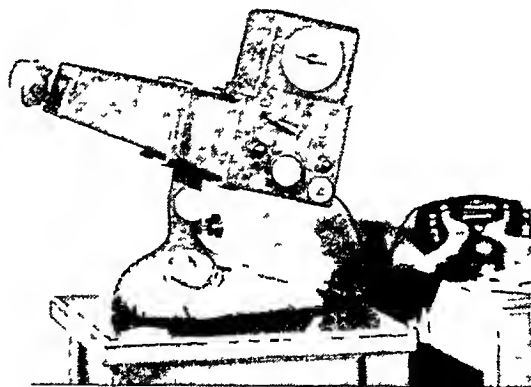
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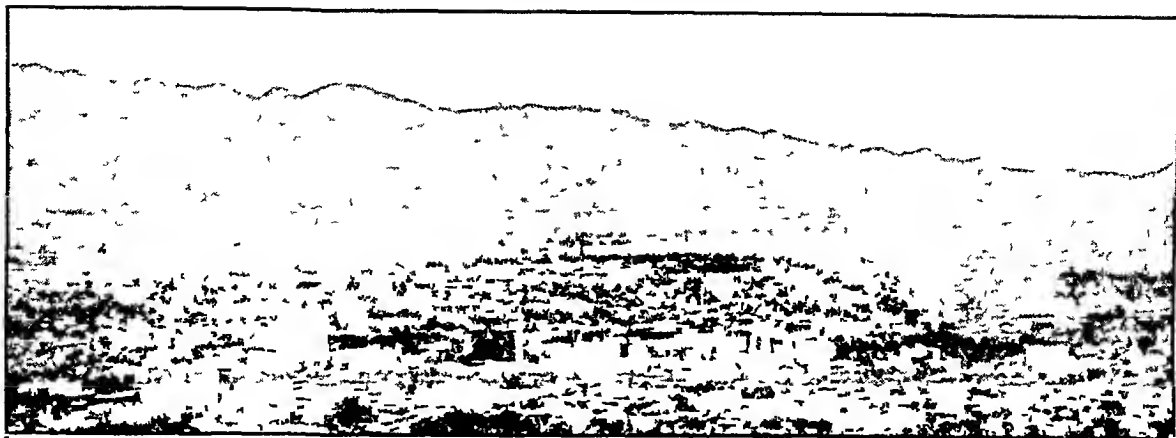
*Jrl A M A 108 451 1937 and 109 756 1937

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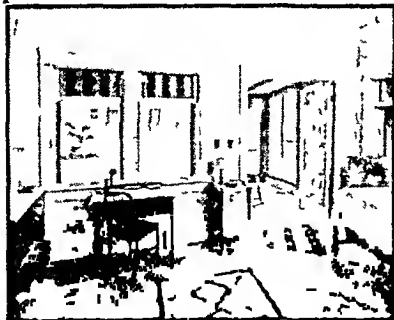
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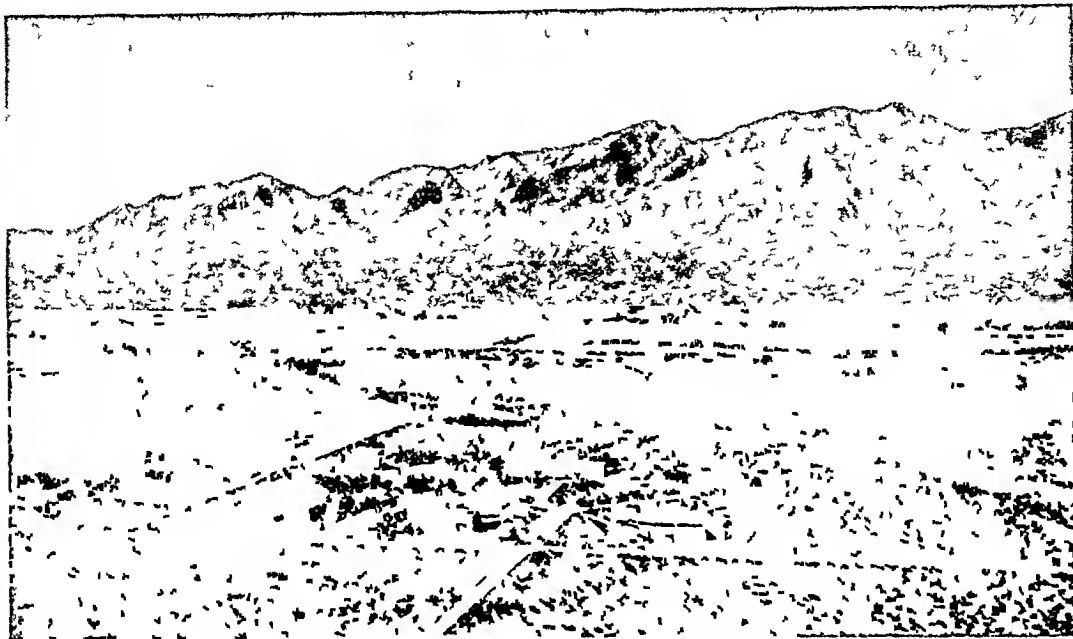


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- 3 Jrl A M A , 110 289, 1938—Editorial, "Nicotinic Acid and Pellagra"
- 4 Editorial, Annals of Internal Medicine, Mar , 1938, pp 1960

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OFFICIAL PERIODICAL OF THE AMERICAN COLLEGE OF PHYSICIANS

Place of Publication—Prince and Lemon Sts, Lancaster, Pa

Editorial Office—University Hospital,
Baltimore, Md

Executive Office—4200 Pine Street,
Philadelphia, Pa

THE ANNALS OF INTERNAL MEDICINE is published by the American College of Physicians. The contents consist of contributions in the field of internal medicine, editorials, book reviews, and a section devoted to the affairs of the College.

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4 Doe, J. E. What I know about it, Jr. Am. Med. Assoc., 1931, xevi, 2006-2008.

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ANNALS OF INTERNAL MEDICINE

VOLUME 11

MAY, 1938

NUMBER 11

THE FUNCTION OF THE COLLEGE

By J H MEANS, M D , F A C P , *Boston, Massachusetts*

I SHOULD like to devote the brief time available for a presidential address to a further consideration of certain questions which I put before you at the dinner last year in St Louis, and which are also closely related to some of the problems raised by Dr Miller in his excellent Presidential Address in Detroit, the year before that

The first of these concerns why we call ourselves a College of Physicians Is there any special significance in the fact that we have selected the appellation College rather than that of Society or Association? What, after all, is a college in the sense in which we have used the word and what is its proper function?

We need not trace the evolution of the term from Roman days to our own We may note, however, in passing that for the most part it has, one way or another, usually been connected with affairs of the intellect, with the efforts of man to improve his mind

In America, colleges have been the forerunners of universities In England, the old universities are made up of many colleges These are both social and educational units In Great Britain there are also the professional colleges, the Royal Colleges of Medicine and Surgery

These last, since they are in some measure the prototypes of our own College, are worthy of scrutiny King Henry the VIIIth, in granting a charter to the Royal College of Physicians of London, said "his main reason was to check men who professed physic rather from avarice than in good faith, to the damage of credulous people, accordingly, after the example of other nations, he had determined to found a college of the learned men who practised physic in London, in the hope that ignorant and rash practitioners might be restrained or punished" (*British Med Jr*, April 3, 1915, p 607)

The English Royal Colleges, in addition to other functions, possess those of licensing boards In 1913, Mr R J Godlee, addressing the American

* Presidential address, delivered at the Convocation of the American College of Physicians, Twenty-Second Annual Session, New York, April 7, 1938

College of Surgeons, at its foundation, on the "Origin and Growth of the Royal College of Surgeons of England" (*Lancet*, 2, 1913, p 1443), remarked that "If you desire that the diploma" F A C S "shall indicate, not only that a man can pass a severe examination, but that he has been thoroughly well trained, you will be well advised to lay down a special curriculum (I speak the word with dread) over and above that required in the ordinary university course, and to frame the examinations on a standard even higher than the highest degree examinations. It is, in my opinion, essential that the examination should be conducted independently of any medical school, and that the examiners should be chosen only from those who are actually engaged in teaching. It is also highly advisable that examiners should, whenever it is possible, be Fellows of your College and that no candidate should be examined by his own teacher."

Neither the American College of Surgeons nor the American College of Physicians can attain to this quasigovernmental status of the British Royal Colleges. They have no charters, royal or otherwise. They are self-appointed and possess constitutions drawn by their founders in place of charters. None the less, through the prestige which they are gaining, they may accomplish in the elevation of professional skill and learning, something akin to what the Royal Colleges accomplish through authority.

It is probably for the best in this country that minimum standards of professional qualifications be set and enforced by the state. It is for the profession voluntarily, through its various institutions, and by the efforts of its individual members, ever to strive far to exceed these minimum requirements. This is in accordance with sound American tradition. The various boards for certification in specialties, like that for internal medicine which is fostered by this College in collaboration with the American Medical Association, are examples of voluntary efforts for improvement in the quality of professional work.

The College, however, must be more than an instrument for raising standards of practice, if it is to deserve the name of College. To be worthy of such a name in truth it must become a breeding place of ideas, a nourisher of learning, a defender of intellectual freedom, a builder of professional morals, a forum in which can be expressed *any* honest opinion relating to the practice of physic in *any* of its aspects, with the assurance that such opinion will receive dispassionate and disinterested attention and study, and that it will be appraised judgmatically in the light of experience. Should the College be merely another medical society, then it is in fact, not a college at all in the highest meaning of the term.

Let us consider for a moment our national medical association and the relation of this College to it. "Organized medicine," the Association has called itself, "the doctors' trust," it has been called by members of the laity, an institution, be it said at once, which has accomplished great good, but one which by reason of its political nature is subject to certain limitations by which, on the contrary, a College such as this one of ours, is not bound. I

apply the term political to the American Medical Association advisedly I use it descriptively, not critically Its organization is patterned somewhat after the political structure of the United States Its relation to state societies is roughly analogous to that of the federal government to the states themselves The behavior of the Association is political It is partisan behavior, it champions a cause At the present time the cause is something close to standpatism But the policy can be changed at any time, if the membership wills it, just as can that of the federal government, if the citizenry wills it At the present time the electorate of the American Medical Association is apathetic and marticulate because it has no issues, no platforms set up to vote for It is allowing the medical politicians to run things about as they please, and official spokesmen, like Jove on high Olympus, to hurl their thunderbolts of wrath at all who differ with orthodox doctrine As no democracy can be healthy without freedom of speech, real issues and an effective opposition party, it is desirable that those who believe in popular government bestir themselves to change this state of affairs The British recognize this need so thoroughly that in Parliament, I am told, they speak of His Majesty's Loyal Opposition .

It is not my intention to devote this address to a critique of the American Medical Association I have said what I have said in order to indicate what I conceive to be the fundamental difference between a college of physicians and a national or state medical society Each has its use, but they are different The college is not in competition with the medical association The college should be the counterpart of the university, not that of the state It is only through general elevation of the cultural level of society that a democracy can rise above mediocrity The germinative centers of culture are the universities This has been so since antiquity They are the noblest institutions of man They stand for no ulterior purpose They are free as no other institutions are free They are committed to no fixed policies other than that of acquiring and disseminating wisdom It should be as unthinkable for us to have a College policy regarding social, economic, political or scientific aspects of medicine as for one of our universities to take sides in a political campaign It should also be unthinkable that we should at any time be unwilling to hear all sides of any problem related to the practice of medicine

We are in great need, as was made clear by Dr Miller in Detroit, of medical statesmen, men of intellectual honesty, breadth of vision, courage, nobility of purpose and the qualities of leadership, who can find the way to the solution of some of the problems of medical service which now baffle both the profession and the public The development of enlightened opposition within the democracy of the national association is one way of bringing to light such leaders, the development of a university atmosphere in a College such as this, is another

The behavior of the College must be that of scholars The College must not seek through propaganda to reach veiled objectives, but rather it must

search for, and broadcast, the whole truth, insofar as it can ascertain it, in all matters relating to the work of the physician. It must set for the profession at large an example of fine professional character. These are its proper functions. It is as desirable that its membership include men of thoroughly diverse opinion as it is that university faculties should do so. We want no society of "yes-men," we want genuine thinkers, and if we have genuine thinkers, we are bound to have diversity of opinion, because, as a speaker, I recently heard, remarked, "the only persons who think alike are those who do not think at all." In this connection, I should like to quote an editorial which appeared in 1933 in the *Lancet* (October 7, 1933, p 812) "From the moment that the idea of any tests or qualifications for university teachers other than those of ability and intellectual honesty is entertained, decay must begin. 'Cleverness, talent, skill, fluency, memory, all these are understood and rated in the market. A cultivated mind just because it is above all price is apt to be overlooked altogether.'" There is an idea here which this College may profitably make use of in selecting its members.

May I return to the American Board of Internal Medicine. This examining body which is the offspring of the College and of the American Medical Association requires that for certification as internists candidates must possess certain qualifications and must have had certain training.

The question arises at once then. Where are they to get this required training? Our sister College, the American College of Surgeons, has concerned itself with this question. Recognizing the internships and residencies of the United States, in a host of hospitals, taken collectively, as one great educational institution, it fancies itself, so far as the training of surgeons goes, as the coordinating, directing and administrative center. To use the somewhat imaginative language of the Chairman of its Board of Regents, the hospitals of the country, which train residents in surgery, are part of the campus of the American College of Surgeons. This may be subjecting the term campus to considerable strain, but none the less the idea is made clear by this wording. The College of Surgeons visualizes itself as constituting, in cooperation with the hospitals, a great college for graduate training in surgery, a training which will make it possible for men to qualify for certification as surgeons by the Board of Surgery. The College of Surgeons, furthermore, has invited the College of Physicians to cooperate with it and to perform in medicine a similar function. To what extent or in what way it is wise for us to do so has not been determined. It is a problem in which the part of wisdom is to proceed carefully. Certainly it is true that whereas the universities of the country have provided well for undergraduate teaching and for medical research, for graduate teaching they have done relatively little. Under these circumstances, there is an opportunity for the Colleges, that of Physicians as well as that of Surgeons, cooperating possibly with hospitals—far better I think with medical schools—to arrange for the continuation of professional training to the highest levels attainable.

The requirements for membership in the College are related to these matters. When the American Board of Internal Medicine successfully establishes itself as the generally accepted agency for certifying internists, then it will be logical for this College to make certification by it, or by an equivalent board in one of the other medical specialties, a prerequisite of membership.

Some of you may recall that at the Boston meeting in 1929, Dr. George Vincent told us we were an elite—a self appointed one at that. He said further that everyone wishes to become a member of an élite. If he cannot get into an existing one, he starts a new one, and after he has got all his friends in, he raises the entrance requirements. He intimated that that is what we have done. The jest is not devoid of application, but this need not depress us. So long as we do it for a high purpose, it is neither dishonest nor hypocritical for us steadily to raise our entrance requirements, even to a point where some of those of us already in could not pass were we to seek to enter now. The significance and usefulness of the College in the intellectual world of our profession will be determined entirely by the mental calibre, the moral fibre and the learning of its members. Anything we can do to elevate these is justifiable, anything we can do to promote the growth of medical scholarship is meritorious. The physician must continue to study throughout his life. The College must be made an instrument to help him do so.

Let us consider for a few moments what may be a proper scope for the deliberations and discussions of the College at its Annual Sessions, its regional meetings, through the medium of its journal, and the informal intercourse among its members. We were told in St. Louis that the doctor should stick to his last, a metaphor intended to mean apparently that we shouldn't bother our heads about anything but the scientific aspects of medicine. The social, economic, political, and even the philosophic aspects are none of our business. I hardly think it is necessary to seek arguments to refute this pronunciamiento. It is palpably as ill balanced as is its opposite which we sometimes hear, that no one but the doctor should have any say in the regulation or method of dispensing medical practice.

The social, economic and political aspects of medicine certainly may rightfully engage the attention of a College of Physicians. That is why I have included, cautiously, a few such items in the present program. They also are of immediate concern to the public, the individual members of which—Johnnie Q., for example—may at any time become patients. Recently they have aroused the interest of both profession and laity to an unusual degree. They have given rise to a considerable amount of somewhat acrimonious discussion. That this should be so is altogether gratifying, for such discussions sometimes clear the atmosphere and thus permit a clearer view. Also there is the possibility that from them will emerge an idea or two, actually constructive.

I will not dwell longer on the social, economic or political aspects of

medicine. Instead, I should like to suggest briefly certain types of philosophical, or at least ethical, problems which I think might advantageously be included from time to time among the topics to be deliberated upon by the College. For example, the question of whose medicine is it? or does the patient exist for the doctor, or the doctor for the patient? The answer to this would seem simple, that the doctor exists for the patient, and yet when we get involved in problems of the provision of medical care, the conditions of medical practice, the methods of paying the doctor, the ethics get very complicated. The practice of medicine—is it a business or a profession? A profession, of course, you'll say, but what's the difference? The motive of business is profit. What is the motive of a profession? Profit also, but not profit alone. The professional man expects, and ought, to earn his living by practicing his profession. The physician wants, and is entitled to, adequate remuneration, but in addition he gets a part of his reward from the intellectual enjoyment which a calling requiring some learning bestows upon him (this reaches its highest pitch when he is able to make an original contribution to medical knowledge) and from the spiritual values which are to be derived from associating in a helpful way with many kinds of people. The profit element and the pleasure element both enter into the motivation of the physician. In considering his behavior and his relations to other classes in the community, it is best to face these facts realistically. It is idle to think of the physician as a consecrated sort of person giving himself idealistically to the cause of suffering humanity. Rarely he may be just that, as occasionally there are saints in other lines of human endeavor, but the rank and file of him are not, nor is it altogether desirable that they should be. If the laity wishes to idealize us, let it do so, but let us not be led from the truth of the situation thereby. As a matter of fact, the laity is more inclined nowadays to damn the doctor than to idealize him, and this is largely due to his inability to make his methods of dispensing medical service as efficient as a streamlined age requires. The layman, who may become a patient, is just as personally interested in the manner of provision of medical care as is the doctor, and I believe that any disinterested judge would say he had as good a right to be. The practice of medicine is the doctor's to make an honorable living by, and ideally to gain some happiness by, it is the layman's to have his health preserved by, the patient's to have his ills relieved by. When the interests of doctors and patients come into conflict, compromises must be reached through the display of fairmindedness on both sides.

We hear a great deal about the sacrosanct doctor-patient relationship. No third party can be allowed to come between the two involved. This has been used as an argument against all attempts to improve the efficiency of medical service through group practice. When it is suggested that a disinterested outside person could with greater equity than the doctor determine what might be a proper fee for services rendered in any given case, there are storms of protest from the conservative wing of the profession.

Yet a philosopher might recognize such an arrangement as an ideal one, and, as a matter of fact, it is actually working successfully in more than one place to the satisfaction of both doctors and patients. Professor Lawrence J. Henderson has considered the doctor and patient as a social system, analogous somewhat to a physico-chemical system, two elements acting upon one another through sentiments. The doctor must seek to influence the patient through the patient's sentiments, and he must take care not to let the patient's sentiments act upon him. In other words, he must keep his own sentiments out of the picture as much as possible. He must perform his professional duty disinterestedly, but if he is wondering all the time what sized fee the patient can pay him, or what sized fee it is fair for him to ask of the patient, how can he remain disinterested? I submit that having a third party determine the size of, and even collect the fee from the patient for the doctor, is not only not an intrusion into the holy doctor-patient relationship, but actually increases the likelihood of the patient's receiving from the doctor the best and wisest treatment the doctor is capable of giving.

Another thing that stimulates the doctor to do his best by his patient is to have his work overseen by his critical colleagues. If this is an intrusion into the holy relationship, then it is to the patient's best interest to have an intrusion. I do not believe that it can be successfully denied that the place where a patient is most likely to have his case diagnosed and treated correctly is in the public wards of a teaching clinic. This is not because the doctors are necessarily any wiser there, but because if one makes a mistake, another will observe and correct it. If one has some new information about diagnosis or treatment that applies to a given case, he will tell his colleagues about it. Why in former times did patients walk from Jerusalem to the Allgemeines Krankenhaus in Vienna? Because they knew that in that center of medical learning they stood the best chance of getting cured.

One other ethical question I should like to indicate. Is it noble or ignoble, is it wise or otherwise, that physicians and surgeons should give their professional services to the care of the indigent? There is also an economic question connected with this matter, but it is quite simple, namely, if doctors are to be paid for caring for the indigent, who is going to pay them? The answer to this is quite obvious. If they are to be paid at all it will have to be by the community because there is no other source. The ethical problem is more puzzling. By tradition, down through the ages, the physician has given his services to the poor. The fact that this has always been so, however, does not of necessity prove either the wisdom or the justice of the custom. Should the physician give his service to the indigent? Is he more obligated to see that the indigent get adequate care than is any other responsible member of the community? He possesses the skill to get them well perhaps, but should he be expected to give this away when other members of the community are making no parallel sacrifice? Of course, other members of the community will readily accept his gift so long as he is willing to make it. But why does he make it? Because it is traditional for him to

make it. Also because he gets a return for it, not in money, but in experience, in the prestige that attaches to a good hospital appointment (the indigent are cared for largely in hospitals), in the pleasure that is to be derived from associating with the other members of the staff of such an institution and, finally, in the spiritual uplift that is to be got from giving of one's self to the service of others.

Whether these rewards are adequate is a fit subject for discussion. Under ideal circumstances, as, for example, in privately endowed teaching clinics, undoubtedly they are. In large publicly supported hospitals, where the pressure of work is great and much of it is of a drudgery type, perhaps they are not. It must be admitted that if the profession should abandon its traditional custom of giving its service freely to the poor, something of an intangible or spiritual nature would be lost. However, we have to face the realities of our own day, and it is not unlikely that in many instances at least the indigent will get better medical service if the community pays for it.

It may be proper to add that even if the doctor is paid for caring for the indigent, he still has the opportunity to exercise his generosity, as does any other citizen, by giving of his substance to the most that he is able to the worthy causes of his community. Let him show the world that the doctor can be as good a citizen as any. Let him also, in rendering the service for which he is paid, add to it those qualities of spirit and purpose which cannot be bought with gold. Therein lies his chance to preserve the ancient values in the face of modern adaptations.

I must now draw this utterance to a close. I have sought to indicate to you my conception of a College of Physicians, of its nature and purpose, of its attitudes and of the scope of its deliberations and activities. In conclusion let me urge all members of the College, especially new members, to put, as members, scholarship first. Let me remind you that scholarship flourishes only in the atmosphere of freedom. There is indeed no place for "yes-men" in a truly learned society, nor is there place for political maneuvering, or reprisal for the expression of honest opinion. Recall the words of Voltaire, "Ecrassez l'infame." The infamy of which Voltaire spoke was religious bigotry. The bigotry of which we stand in dire peril today, as President Conant pointed out at the Harvard Tercentenary, is political bigotry. Let us strive, therefore, in this propaganda-poisoned world, to keep our land a free democracy and within it to make our College take on the essence and spirit of the university and thus become an instrument of service to humanity.

NEW EXPERIMENTAL DATA ON ARTIFICIAL HYPERTHERMIA

By A BESSEMANS, M D , Ghent, Belgium

GIOVANNI Truffi recently reported that *Treponema pallidum* remains virulent when passed for one hour through the body of birds, which are supposed to have a body temperature of 42° C (107.6° F). Mario Truffi and Beck theorized on these results, and reached the bizarre conclusion that *Treponema pallidum* could resist, within the organism of birds, temperatures of 42° C (107.6° F) during at least five hours. They deduced from the experiments of Giovanni Truffi that mere thermic rise is not the cause of the action of malaria therapy and of pyretotherapy in general.

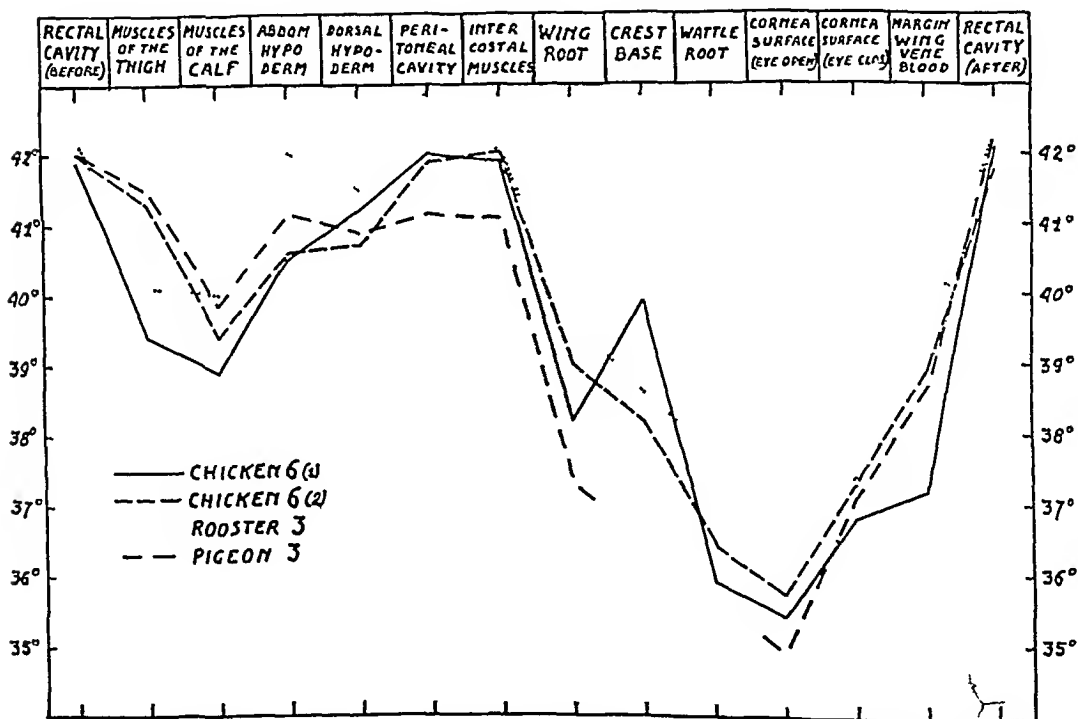


FIG 1 Examples of superficial and deep tissue temperatures in birds (2 chickens, 1 rooster and 1 pigeon)

We believe that we have disproved these assumptions. We have repeated the experiments of Giovanni Truffi, and have accurately measured, by means of thermocouples, the temperatures of various parts of the animal body during experiments involving ten hens, three roosters and eight pigeons. In the first place, as is shown by the accompanying graph (figure 1), the temperatures of various parts of the bodies of these animals vary

* Presented at the St. Louis meeting of the American College of Physicians, April 21, 1937.

From the Institute of Hygiene and Bacteriology of the State University of Ghent, Belgium

tremendously, notably from 35° C to more than 42° C (95° F to 107.6° F). Hence, if treponemas lodge in cool parts, they may retain their virulence. Secondly, we believe that the experiments of Giovanni Truffi must have been carried out under peculiar conditions, because we were not able to confirm his results.

The blood, as well as emulsions of the liver, spleen, brain, spinal cord, and several lymph nodes of our 21 experimentally infected birds, failed to produce a single syphilitic lesion, when injected into the testicles of 42 rabbits which survived for at least four months. The popliteal lymph glands of these rabbits also remained sterile.

Furthermore, we must call attention to the fact that, as a syphilitic strain is passed through a series of rabbits, it gradually becomes more virulent for this animal. It is not far afield to assume that this is connected with an increased resistance of the strain to temperature. Giovanni Truffi worked with a strain which had serially passed through the bodies of hundreds of rabbits, since it was isolated about 30 years ago. As our own strains have aged, they have become more virulent. In some cases also, they seemingly have become more thermo-resistant. In 1928 we were able to prevent the appearance, or to cure syphilomata of rabbits in 7 out of 13 experiments, by transposing the testicles for several hours into the abdominal cavity (table 1). In 1935 (same table), this was possible in only three out of 22 experiments.

We have shown that there is a considerable variation of the temperature of different parts of the body of normal birds. Tables 2 and 3 show that this variation also exists in the organs and tissues of normal rabbits. It should be noted (table 3) that there is a variation of more than two and a half degrees centigrade (5.5 degrees Fahrenheit) in the temperatures of such a small organ as the eye of this animal. Even when hot baths are given to a rabbit (table 4), there is a variation of temperature in the various parts of the body.

Table 5 shows that the position of the active and of the inactive electrode, during local diathermy of the deep organs of the true pelvis, has a decided influence on the temperature obtained in the cervix (6 to 14 measurements were made on each of 12 women, to obtain the averages recorded in the last column).

Analogous variations with the mode of application were observed, during local diathermy, in different parts of the abdominal cavity of the rabbit. This was accomplished by means of accurately calibrated thermocouples, inserted through the anal opening, as is shown by the roentgen-rays (figures 2 and 3).

When temperatures are measured in the electrical or electromagnetic high frequency fields, the latter must be discarded if resistance pyrometers or thermocouples are used. Mercury thermometers are only reliable, within the fields, when inserted into the tissue. On the contrary, quartz and even

TABLE I
Temporary Ectopisings, into the Abdominal Cavity, of Rabbits' Testicles Inoculated with Syphilis or Carriers of Syphiloma Nodules*

Case	Trepo nemas before	Duration of displacement (in days and hours)	Extreme rectal temperatures (in degrees centigrade)	Results				Transfer of the lymph glands	Remarks
				Treponemas (by puncture)		Clinical aspect			
				Immediately	Later	Immediately	Later		
A EXPERIMENTS MADE IN 1928-29 immediate displacement after inoculation									
1	(L)	51 d	38 7-39 6	Absent	Absent	N	Normal		Control (R) P
Displacement of syphiloma nodules									
2	P	3 d	38 8-39 7	P mobile	Immobile 5th day	P	N 13th day	P	
3	P	3 d	38 5-39 3	P immobile	P mobile	P	Evolution P		
4	P	2 d	38 5-39 3	P mobile	Immobile 4th day	P	N 21st day		
5	P	2 d	38 6-39 4	P mobile	P mobile	P	Evolution P	P	
6	P	24 h	38 9-39 8	P mobile	Immobile 3d day	P	N 14th day		
7	P	24 h	38 9-39 9	P mobile	Immobile 3d day	P	N 13th day		
8	P	24 h	38 5-39 3	P mobile	P mobile	P	Evolution P		
9	P	12 h	38 7-39 4	P mobile	P mobile	P	Evolution P		
10	P	12 h	38 6-39 6	P mobile	P mobile	P	Evolution P		
11	P	7 h 30 m	38 6-39 5	P mobile/agon	Immobile 24th hour	P	N 11th day		
12	P	6 h	38 6-39 7	P mobile	P mobile	P	Evolution P		
13	P	3 h	39 5-40	P immobile	N 24th hour	P	N 4th day		
B EXPERIMENTS MADE IN 1935-36 immediate displacement after inoculation									
14		8 d	38 6-39 5	Absent	Absent	N	Normal	P	Late enteritis
15		7 d	38 7-39 6	Absent	Absent	N	Normal	P	
16		5 d	38 6-39 4	Absent	P (autopsy)	N	Normal		Death the 5th day
17 to 35		1 to 8 d	38 4-39 7	Absent	P	N	Evolution P		

* P = positive, N = negative, U = left, R = right, agon = agonizing

TABLE II
Average Temperatures (in Degrees Centigrade) of Various Organs and Tissues, in the Normal Rabbit

Organs and tissues	First series of measurements	Second series of measurements
Axillary glands	39.7	—
Rectum	39.48	39.80
Liver	—	39.69
Lungs	—	39.29
Upper cervical vertebrae	39.16	—
Testicle displaced into abdominal cavity	39.05	39.28
Costo chondral articulation	39.04	39.46
Muscles of the abdominal wall	—	39.37
Occipital periosteum	39.01	—
Sternum	38.99	—
Skin of the abdominal wall	—	38.73
Parietal periosteum	38.62	38.18
Brain	—	38.45
Mouth cavity	38.28	39.35
Submaxillary glands	38.24	—
Inguinal glands	38.15	38.32
Retina	38.10	—
Popliteal glands	38.08	38.88
Testicle, 1 min. after replacement	37.92	38.05
Dorsal skin	37.91	—
Frontal periosteum	37.90	37.25
Testicle, 2 min. after replacement	37.44	37.89
Skin of the base of the ear	37.42	37.69
Subarachnoidal cavity	—	37.35
Hip muscles	—	37.34
Skin of the lower eye-lid	—	37.07
Caudal vertebrae	37.05	—
Nasal bone	36.98	35.59
External malleolus	36.77	—
Testicle, 5 min. after replacement	36.74	36.97
Tarsus	36.45	—
Skin of the middle of the ear	—	36.00
Genital mucosa	—	35.93
Center of the cornea (eye open)	35.93	35.50
Metatarsus	35.17	—
Phalanges	34.41	—
Subungual skin	—	34.20

TABLE III
Average Temperature of Different Parts of the Eye, in the Normal Rabbit

Place of measurement	Degrees centigrade
Vitreus	38.3
Retina	38.1
Sclera	37.4
Anterior surface of the iris	37.2
Bulbar conjunctiva	36.8
Palpebral conjunctiva and posterior surface of the nictitating membrane	36.7
Posterior surface of the cornea (between center and periphery)	36.6
Upper eye lid (4 mm. depth)	36.6
Anterior surface of the nictitating membrane	36.5
Upper eye-lid (average)	36.0
Cornea (average)	36.0
Center of the anterior surface of the cornea	35.8
Periphery of the anterior surface of the cornea	35.7
Cornea (between center and anterior surface)	35.5
Upper eye-lid (2 mm. depth)	35.4

TABLE IV

Temperatures (Degrees Centigrade) Simultaneously Measured at 5 Minute Intervals, for Different Parts, in 2 Normal Rabbits Treated by Hot Baths

Bath water	Testicle kept exterior	Rectal cavity	Right popliteal gland	Left popliteal gland	Mouth cavity	Right axillary folds	Left axillary folds
<i>First experiment</i>							
42 6	40 4	39 4	40 6	40 4	38 1	38 8	38 8
42 5	40 4	39 9	40 4	40 8	38 6	38 6	38 6
42	40 8	40 7	40 8	41 6	39 1	39	39 4
41 5	40 8	41 1	40	41	39 2	39 2	39 4
42	40 8	40 8	40 4	40 8	39 7	39 2	39 2
42	40 4	40 9	40 4	40 4	39 7	39 6	39 6
42	40 4	41 1	40 4	40	39 8	39 2	39 6
42	40	41 1	40 4	40 4	39 9	39 6	39 8
42	39 8	41 1	40	40	40	38 8	39 2
42	40	41 1	40	40	39 9	39 2	39 2
<i>Second experiment</i>							
42 3	41 4	39 4	40 2	40 6	38 2	39	39
42	41 8	40	41 6	41 8	38 4	39 8	39 8
41 5	42 2	39 7	41 8	42 2	38 5	40	40 2
41 5	42 2	40	42	42 4	38 8	40 4	40 4
41 8	42 2	40 1	42 4	42 4	38 8	41	40 6
42 1	42 6	40 1	42 4	42 6	39	40 6	40 6
42	42 2	40 2	42 2	42 4	39	40 2	40 2
42	42	40 3	41 6	42 6	39	40 2	40 6
41 8	41 4	40 3	41 8	41 6	39 1	40	40 6
41 8	41	40 3	41 8	41 8	39 2	40 2	40 2

TABLE V

Average of Maximum Temperatures Reached by Cervix Uteri, in Women, during Medium Wave Diathermy of the Deep Organs of the True Pelvis

Location of active electrode	Location of inactive electrode	Relative size of the two electrodes	Different groups of cases	Calculated average temperature (degrees centigrade)
Above symphysis	Buttocks	1/3	27 to 29	221 88/6 = 36 98
id	id	1/2	30 to 36	525 68/14 = 37 55
Across the lower abdomen	id	2/3	42 to 44	228 14/6 = 38 02
Above symphysis	id	2/3	37 to 41	380 3/10 = 38 03
Across the lower abdomen	id	1/1	45 and 46	152 9/4 = 38 22
Vagina	Iliac fossae	1/5	1 to 4	317 54/8 = 39 69
id	Above symphysis	1/7	5 to 8	323 75/8 = 40 47
id	Buttocks	1/7	16 to 19	325 61/8 = 40 70
id	id	1/6	14 and 15	163 7/4 = 40 75
id	Across the lower abdomen	1/11	9 to 13	409 1/10 = 40 91
id	Buttocks	1/12	23 to 26	328 76/8 = 41 09
id	id	1/11	20 to 22	246 6/6 = 41 10

glass thermometers filled with benzene or with mineral oil are never affected (Such thermometers may be of the ordinary, curved or Zondek type) For instance, when placed in the open air between the electrodes of short or



FIG 2 Roentgen-ray of a rabbit, in which a thermo-electric tube was introduced through the anal opening until a definite resistance was met the end reaches the left hypochondrium

ultra-short wave apparatuses, or surrounded by the coil of an "inductotherm," they do not record a fall of the temperature directly after the current has been turned off Figures 4, 5 and 6 show syphilitic rabbits being treated by a "diathermax" apparatus (medium waves), an "inductotherm" (short

waves) and an "ultrapandoros" (ultrashort waves), the temperature of a syphiloma or a popliteal lymph gland, of the neighboring air, of the mouth and the rectum being measured, in the course of the experiments, with the

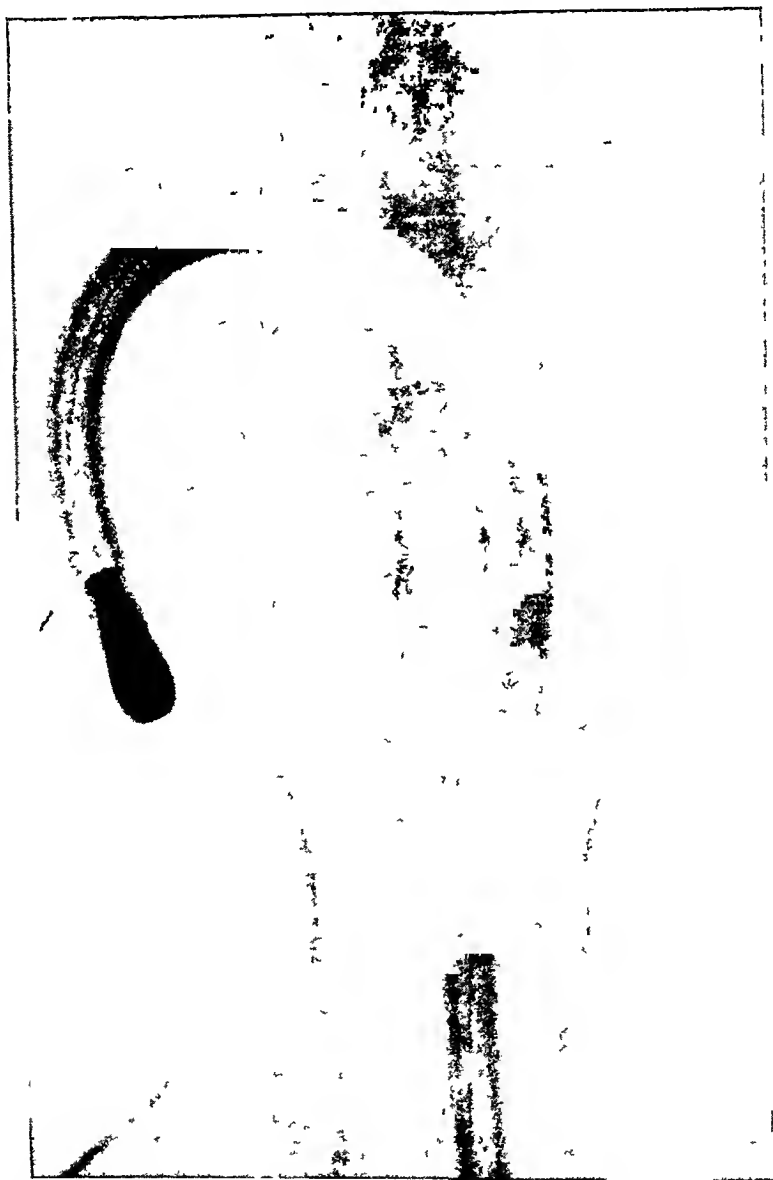


FIG 3 Same roentgen-ray as in figure 2, the tube having been pushed farther the end bends towards the left iliac fossa

benzene or mineral oil thermometers, without it being necessary to turn off the current

In these cases, there is a great variation of the temperature of the measured infected regions (syphilomas and popliteal lymph glands), as long as they are not covered. On the contrary, if in similar experiments these

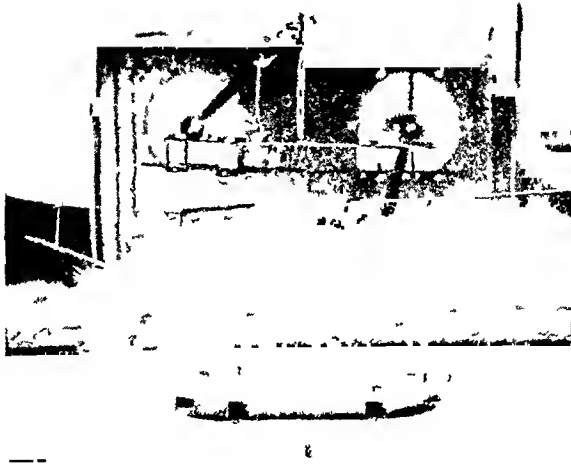


FIG 4 Comparative thermic measurements of a left testicular syphiloma in the rabbit, of the neighboring air and of the rectum, in the course of a treatment by a "diathermax" apparatus (electric short wave diathermy of 18 meters) applied bipolarly the special Zondek thermometer was placed within the syphiloma



FIG 5 Comparative thermic measurements of a left popliteal lymph gland in the rabbit, of the neighboring air and of the rectum, in the course of a treatment by an "inductotherm" (magnetic short wave diathermy of 25 meters), the cable forming a solenoid around the body, the special Zondek thermometer was placed within the tissue at the level of the gland

regions are insulated against heat-loss by covering them with cotton, high local temperatures can regularly be obtained

Some animals die of heat stroke during such experiments. But if the temperature of a testicular syphiloma is raised to 42°C (107.6°F) for one hour by this method, a destruction of the syphilitic germ in the organ usually results, this is frequently not the case when a same temperature is produced in a popliteal lymph gland

Thus, in our experience, the increased thermo-resistance "in vivo" of the treponemas of the superficial lymphatic system of the rabbit also exists against short and ultrashort wave radiation. Besides, neither the wave length nor the physical modality used has any effect *per se* on killing the

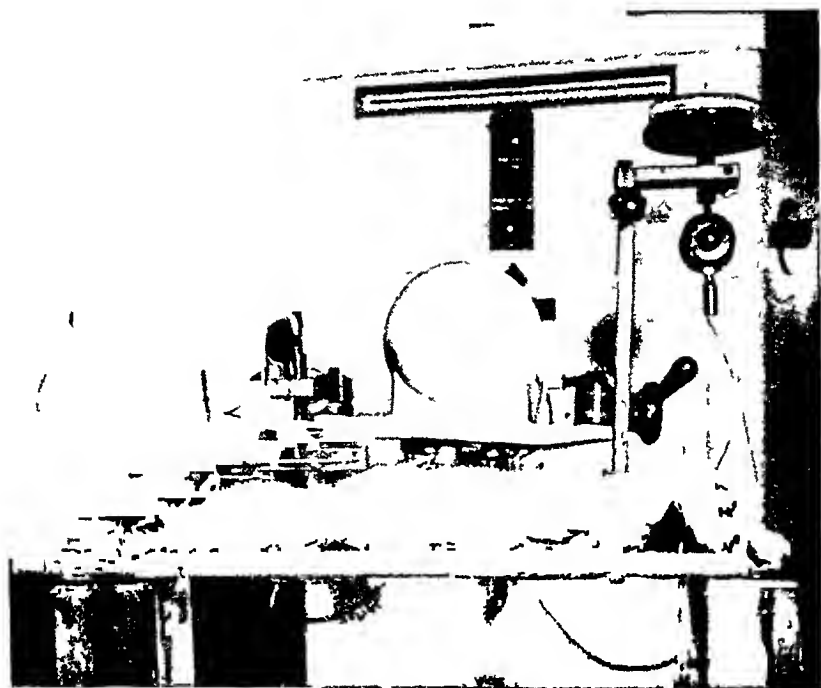


FIG 6 Comparative thermic measurements of a left testicular syphiloma in the rabbit, of the neighboring air, the rectum and the mouth, in the course of a treatment by an "ultra-pandoros" (electric ultrashort wave diathermy of 4 meters), applied monopolarly the special Zondek thermometer was placed within the syphiloma

treponemas, the important factor is the height of the temperature of the lesion

It is well known that if a rabbit with a testicular syphiloma is immersed in a hot bath, the syphiloma disappears under definite conditions of temperature and time. If the entire animal develops a sufficiently high fever as a result of the hot bath and if the infected testicle does not come in contact with the water, its syphiloma heals or not, according to whether it is surgically fixed within the abdominal cavity, or is in a position where it is kept cool. This disproves the rather absurd claim advanced many years ago, that water has anything to do with healing syphilis. It proves that the favorable healing effects are caused by heat,

We have also demonstrated that in man, whatever are the physical heating procedures used, neither the mobility nor the virulence of the treponemas nor the clinical aspect of the syphilitic lesions is affected, if the local temperature is not high enough. The exposure of a lesion to an intense electric field does not produce any changes, even if the intensity is so strong as to burn the superficial tissues.

Finally, we have experimented "in vitro" with an emulsion of an Ehrlich sarcoma of the mouse, with various bacterial cultures, and with an emulsion of guinea pig blood rich in trypanosomes. If any of these products are exposed to the action of short or ultrashort waves, a sterilization can be obtained. If, however, the test tubes containing the products are cooled at the same time by means of air or flowing water, this is not true, if the temperatures of the emulsions and cultures are kept low enough to prevent the thermic action of the electric waves. Therefore, it is apparent that, in these experiments also, we are not dealing with any specific wave effect. As an example, table 6 proves this fact for *Trypanosoma gambiense*, treated by short magnetic waves.

There are some paradoxical facts which we have recently observed when heating testicular syphilomas of rabbits by means of certain medium diathermic currents. It sometimes happens that, even if local temperatures which should be adequate for healing the lesion are applied, no healing effect is obtained. It also happens occasionally in this treatment that if a lesion is cooled by air-blowers to such an extent that no healing should result, the treponemas nevertheless disappear, and the lesion heals after a few days.

TABLE VI

Influence of Short Magnetic Waves of 25 Meters ("Inductotherm") on an Emulsion of Guinea-Pig Blood Very Rich in Trypanosomes (Arsenoresistant Strain of *Trypanosoma gambiense*)

Duration of irradiation (in minutes)	Temperature (in °C) of emulsions	Density in mobile Trypanosomes	Aspect of parasites
<i>A Maximum diathermy without cooling</i>			
60	34	+++	Very mobile
90	39	+++	id
115	43	++	Less mobile
120	44.5	+	Some moving slowly, some already dead
125	46	—	All dead
130	47	—	Lysis *
<i>B Same diathermy but with cooling</i>			
0	20	+++	Very mobile
60	30	+++	id
120	32	+++	id
160	33	+++	id †
<i>C Emulsion kept, without being irradiated, at room temperature</i>			
300	20.5	+++	Very mobile

* Inoculation in the guinea-pig negative

† Inoculation in the guinea-pig positive and persistence of arsenoresistance

These paradoxical reactions may possibly be explained by a change in thermo-resistance of the germ, by some effect of high frequency currents on the neuro-vegetative system of the rabbit, or by other as yet unknown factors. The reaction of the whole organism becomes evident in these cases. At present such observations are confined to the rabbit.

Following the ideas of Walter M. Simpson and Clarence A. Neymann that a judicious combination of chemotherapy and pyretotherapy might accomplish more than if either therapy is used alone, we devised a method by which rabbits could be treated with artificial fever and appropriate chemical substances. A cabinet was constructed of wood, without the use of nails or metal parts. The animal was heated in this cabinet by hot air alone (figure 7) or by hot air combined with electromagnetic induction (figure 8).

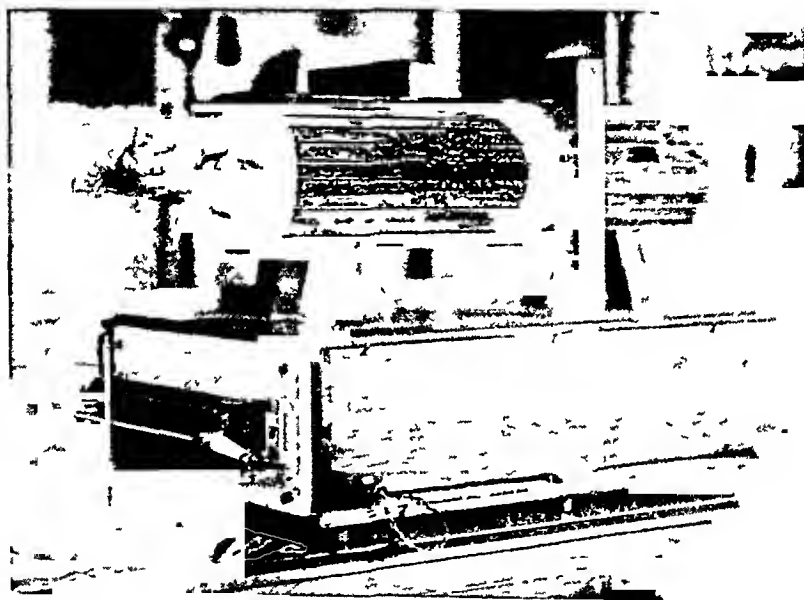


FIG 7 Special heating cabinet for general aero-pyrexia in the rabbit

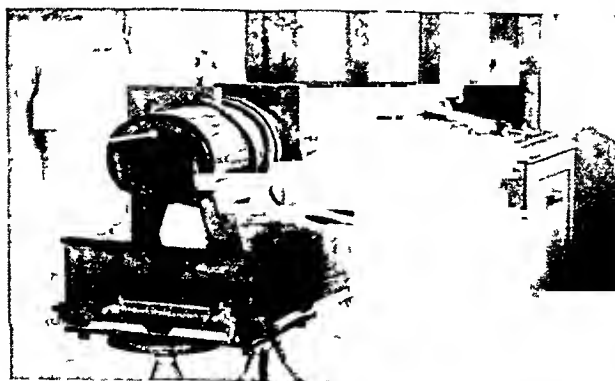


FIG 8 The same cabinet as in figure 7, with the cable of an "inductotherm" wound around it, for general aero-inductopyrexia in the rabbit

If an alone was used for heating, we began with a temperature of 55° C (131° F), and continued at about this level until the rectal temperature reaches 41.5° C (106.7° F), at this point the temperature of the air of the cabinet is reduced to 42° C (107.6° F)

By careful technical manipulation of the an temperature and the intensity of the magnetic field, the rabbits' fever may be maintained at approximately 42° C (107.6° F) for one-half hour. The rabbit is more sensitive to artificial fever than man, probably because of its deficiency in perspiration. It was, therefore, impossible to maintain the temperature for as long a period as has been possible in man.

Nevertheless, an average temperature of more than 42° C (107.6° F) was reached in 11 rabbits which survived. Six of these animals were treated with artificial fever alone, while five were treated with artificial fever combined with arsphenamine. For purposes of comparison, 5 rabbits were treated with the same doses of the drug without fever.

The results appear in table 7. The lymph gland transfer into the testicles of a new series of rabbits was positive in 2 of the 5 animals treated only with arsphenamine. Two of the 6 rabbits treated with fever alone also gave positive transfers. As yet we have not been able to secure positive transfers from any of the 5 rabbits treated with fever and arsphenamine.

TABLE VII
Physiothermo- and Chemotherapy, Single or Combined, of Rabbits Recently Cured of Testicular Syphilomas

Rabbits	Age of syphilis at the beginning of treatment	General hyperthermia				Number of injections of 0.25 cc of solusal varsan per Kg	Lymph gland transfer	
		Number of heatings	Intensity of each heating				Time after the end of treatment	Result
			Duration	Extreme temperatures (in degrees centigrade)	Average temperature (in °C)			
<i>Solusarsan therapy</i>								
1	4 months	—	—	—	—	3	1 month	N
2	id	—	—	—	—	3	90 days	P
3	id	—	—	—	—	3	2 months	P
4	id	—	—	—	—	3	2 months	N
5	id	—	—	—	—	3	3 months	N
<i>Aerothermotherapy</i>								
6	4 months	3	30 min	42 1/42 7	42.5	—	1 hour	P
7	6 months	3	id	42 1/42 8	42.4	—	90 days	N
8	id	3	id	42 3/42 6	42.5	—	2 months	N
9	id	3	id	42 2/42 5	42.3	—	6 months	N
<i>Inductotherm with the air at about 42°</i>								
10	4 months	3	30 min	42 1/42 6	42.5	—	1 hour	N
11	id	3	id	42 4/42 7	42.6	—	8 days	P
<i>Combined treatment</i>								
<i>Aerothermotherapy and solusarsan-therapy</i>								
12	4 months	3	25 min	42 3/43	42.5	3	1 hour	N
13	8 months	3	30 min	42 1/42 5	42.2	3	2 months	N
14	id	3	id	42 1/42 9	42.3	3	6 months	N
<i>Inductotherm (with the air at about 42°) and solusal arsan therapy</i>								
15	4 months	3	25 min	42 1/42 8	42.4	3	11 days	N
16	5 months	3	30 min	42 1/42 6	42.2	3	2 months	N

(*) P = Positive N = negative

We realize that these results are inconclusive. First of all, not enough experimental data are available. Secondly, not enough time has elapsed, either between the end of the treatment and some of the transfers, or since the transfers were made. Thirdly, negative results of lymph gland transfers, even when made in optimum conditions, are not absolutely conclusive. We are now working with a larger series. We believe, however, that the results achieved thus far are suggestive.

We have not employed serological tests for our rabbits because, as has been shown in our previous publications, rabbits, when infected only with the pallidoid treponema (*Spinochaeta cuniculi*), may give positive serological tests. Syphilitic rabbits may give negative tests. Normal rabbits may even give positive tests. Serological tests are, therefore, valueless in this species.

CONCLUSIONS

1 The ideas advanced by Giovanni Tuffi that the *Treponema pallidum* remains virulent after passage for one hour through the bodies of birds have been disproved.

2 The position of the active and of the inactive electrode during local diathermy of the abdominal organs, in the rabbit and in man, has a decided effect on the deep temperatures reached.

3 Quartz or glass thermometers filled with benzene or mineral oil can be employed for the measurement of temperatures in high frequency fields. Such thermometers are not affected by electromagnetic waves.

4 There is a difference "in vivo" in the thermo-resistance of the *Treponema pallidum* of the external syphilitic lesions of rabbits and man, compared with the treponemas found in the lymph glands of syphilitic rabbits. In the latter case the thermo-resistance is so great that it surpasses that of the organism of the host.

5 Neither the wave length nor the physical modality used has any effect *per se* on killing the *Treponema pallidum* within the tissues. The important factor is the height and duration of the temperature of the lesion. The healing effect must be considered in the light of the temperature variations which exist in various parts of the animal body.

6 Paradoxical and unexplained results after treatment with diathermy occasionally occur in rabbits. This is a sign of the reaction of the animal organism as a whole.

7 If bacterial cultures, treated "in vitro" with intense short or ultra-short wave radiation, are cooled so that no heating effect results, they are not affected. The same fact applies to emulsions of an Ehrlich sarcoma of the mouse, and to trypanosomas.

8 A judicious use of the combination of chemotherapy and pyretotherapy seems to be more effective in the syphilitic rabbit than when either therapy is used alone. Serological tests for syphilis are valueless criteria in judging the presence, the progress or the persistence of the disease in rabbits.

DRUGS IN THE TREATMENT OF HEART DISEASE *

By ROBERT L. LEVY, M.D., F.A.C.P., *New York, N. Y.*

"THE following remarks consist partly of matter of fact, and partly of opinion. The former will be permanent, the latter must vary with the detection of error, or the improvement of knowledge. I hazard them with diffidence, and hope they will be examined with candour, not by a contrast with other opinions, but by an attentive comparison with the phenomena of disease." With this paragraph, William Withering, in his *Account of the Foxglove*, published in 1785, opens the chapter dealing with "Practical Remarks on Dropsy, and Some Other Diseases" ³⁶ Certainly, there could be no more appropriate comment with which to begin this discussion.

In any therapeutic program, the use of drugs is but one form of procedure. In the treatment of cardiac disorders, medicinal remedies play an important part because in many conditions they are strikingly effective, often their proper use is responsible for the saving of life. They serve three main purposes: (1) to cope with acute upsets, (2) to restore the function of a failing heart and to maintain it at the optimum level of competency, (3) to prevent the occurrence of disturbances in the circulation, or their recurrence once they have appeared and been adjusted. Numerous remedies have been proposed and tried. Some have stood the test of clinical usage, others, though of proved value, have been supplanted by better drugs which newer studies have made available, many have been found wanting and have been discarded.

It would be neither feasible nor profitable to attempt, at this time, a consideration of all medicinal substances which are known to have an action on the circulation. A few of the more important have been selected which, in the light of current concepts, are regarded as exerting a beneficial action. In its presentation, the material has been divided according to various clinical conditions which can be aided by drug therapy rather than, primarily, into groups of drugs. Although, in some instances, this method calls for repetition, it seems of more practical value, for even though the same remedy may be discussed more than once, the indications for its employment often vary, as well as the manner in which it is best given.

MYOCARDIAL INSUFFICIENCY

Digitalis ²⁴ When symptoms and signs indicate that the heart has failed to function adequately as a pumping mechanism, the administration of digitalis is indicated. This statement holds true, regardless of the

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etiological type of cardiac disease, nor does it matter whether failure is predominantly of the left or the right ventricle. Many of the older clinicians believed that the foxglove was effective only when the auricles were fibrillating, but accumulated experience has proved that an equally beneficial result is obtained in the presence of regular, sinus rhythm.

The mode of action of digitalis on the heart has been the subject of much study. It exerts its influence in part through a direct effect on the cardiac muscle, and in part by stimulation of the vagus nerves. The myocardium reacts by an increase in the amplitude of ventricular contractions. In the normal person, the size of the heart becomes smaller and cardiac output is decreased. In patients with congestive failure digitalis also brings about diminution in cardiac size, but when the heart is dilated, shortening of the muscle fibers is accompanied by increased cardiac output and hence, improvement in the state of both pulmonary and systemic circulations.^{29 31}

The effect on the auriculoventricular conduction system, which, in cases of auricular fibrillation is responsible for slowing of ventricular rate and, in those with normal rhythm, may cause varying degrees of heart block, is due to a double action. There is depression of the junctional tissues and vagal stimulation. Both of these effects can be demonstrated by observing the response to atropine after giving digitalis to patients with auricular fibrillation. There is partial release of the vagus, with increased ventricular rate, but the level of tachycardia is not as high as before digitalis was given, and the effect on the T-wave of the electrocardiogram persists.

When regular rhythm prevails, the heart rate is not slowed by a direct action. One of the compensatory mechanisms for maintaining the circulation when the heart has failed, is acceleration of rate. When ventricular discharge is increased, there is no longer need for this reflex mechanism to operate, with adjustment of the circulation, the heart beats more slowly. Nor is any specific change induced upon either systolic or diastolic blood pressure, such alterations as may occur are due to modifications in general circulatory dynamics. Hypertension, therefore, is not a contraindication to the use of digitalis, frequently, with the relief of heart failure, the level of the pressure becomes lower.

The diuresis which occurs after digitalis administration is not due to stimulation of the renal epithelium. It is the result of improvement in the general circulation. Venous stasis in the kidneys is relieved and an adequate flow of blood through them is resumed. This point must be kept in mind in relation to the use of diuretics.

The choice of a preparation is of some importance. The chemistry of the digitalis bodies is still imperfectly understood. Various glucosides have been isolated and numerous so-called "purified" substances are on sale. There is no better form of digitalis for oral use than the whole leaf, dispensed as tablet, pill or capsule. The tincture, even though active, has an unpleasant taste and necessitates careful measurement of each dose. The discrepancy between the volume of the drop and the minim makes for con-

fusion and uncertainty. The infusion, because of its instability, has been generally discarded. For intramuscular or hypodermic injection, liquid preparations are marketed in ampules, which should be of hard glass to prevent deterioration. Soft glass yields alkali which, in time, renders the contents inert.²¹ On those rare occasions when intravenous injection seems imperative, crystalline strophanthin is the drug of choice.

Biological standardization of digitalis products, necessary because an accurate method of chemical assay is not available, has become the usual practice with manufacturers. Although the one-hour frog method is still recommended in the U. S. Pharmacopoeia, some modification of the intravenous cat method, introduced by Hatcher and Brody in 1910, has come into widespread usage and is generally favored. Approximately 0.1 gm ($1\frac{1}{2}$ gr) of powdered leaf, 15 minims (1 cc) of tincture and 0.1 mg ($\frac{1}{60}$ gr) of strophanthin are equivalent to 1 cat unit, as commonly prepared. Dosage is expressed in terms of cat units. Assay on animals is far from ideal. The results are not always transferable to man because of variability in absorption and because biological activity and therapeutic potency do not always parallel each other. It is the best method now known and has served to do away with the gross variations in strength which, twenty-five years ago, made even approximate dosage entirely a matter of trial and error.

When possible, it is best to give digitalis by mouth. The oral route is simple, safe and efficacious. If the dose is adequate, a beginning effect on the heart can be obtained in from two to five hours, a maximal effect in from six to twelve hours. In the presence of nausea or vomiting, or after surgical operation, digitalis may be administered by rectum, as the tincture, or in a suppository.¹⁹ Absorption is good and the speed of action is comparable to that observed when similar doses are given by mouth. Intramuscular injections may be made when the oral and rectal routes are not available. Intravenous injection is always attended with some hazard. A high level of concentration is quickly attained and the margin between therapeutic and toxic dose is relatively small. Intravenous injection should never be made if the patient has received digitalis within the preceding week, because of the danger of cumulative effect. Introduction of a digitalis body directly into the circulation is rarely necessary and should be done only in emergencies. As a rule, if the need seems immediate, digitalis will not avail.

The optimal total therapeutic dose varies according to the degree of cardiac insufficiency and the susceptibility of the individual. In general, the more advanced the failure, the greater is the amount required. The total dosage for inducing full effect in a person who has not previously received digitalis within two weeks is between 1.0 and 2.0 gm (15 and 30 gr). It is usually safe to administer 1.0 gm in divided doses during the first 24 hours, these may conveniently be given at intervals of four or six hours. In the second 24 hours, 0.5 gm may be given in divided amounts at similar intervals. Subsequent therapy depends upon the effects obtained and those

regarded as desirable. If haste is not necessary, smaller amounts may be given over a longer period. Relatively large doses are tolerated by children.

After the restoration of compensation, it is often of advantage to continue each day the administration of small maintenance doses over a period of weeks, months or years. This is almost invariably necessary in patients with permanent auricular fibrillation, in order to keep the ventricular rate at a properly low level. The optimum rate must be determined in each case but is usually between 70 and 80 per minute, at rest. A daily ration is useful also in older persons with enlarged hearts, in them a continued "tonic" effect may prevent the recurrence of failure, particularly if the amount of cardiac reserve is small. Digitalis disappears from the body, either by elimination or destruction, at the rate of approximately 0.1 to 0.2 gm (1½ to 3 gr) in 24 hours. But as little as 0.05 gm or as much as 0.3 gm daily may, on occasion, be the dose required for holding a continued effect at the desired level. Each patient, in this respect, is the subject of experiment.

Calculation of dose according to body weight is not necessary. It affords to the physician a false sense of accuracy based on a formula which is subject to a wide margin of error. Skillful use of digitalis requires careful study in every case. Standardization of the drug and the establishment of satisfactory clinical criteria for therapeutic action have, in large measure, eliminated the necessity for inducing toxic effects in order to be certain that enough has been given. The oft quoted dictum of Withering—"let it be given until it either acts on the kidneys, the stomach, the pulse, or the bowels"—no longer holds good with respect to stomach and bowels. Deliberately to poison the patient is not the goal of modern therapy.

Yet, in spite of reasonable care, toxic effects occasionally are induced. They must be watched for and, immediately upon the appearance of one of them, the drug should be discontinued or the dosage curtailed. Nausea, vomiting, headache, diarrhea and the occurrence of premature contractions are among the earlier evidences of intoxication. Mental confusion and visual disturbances are less frequently encountered. In the more advanced stages of poisoning, auricular fibrillation, auriculoventricular heart block and ventricular tachycardia may occur. Ventricular tachycardia is of particular significance, for giving more digitalis, after it has appeared, can convert it into ventricular fibrillation and cause sudden death.

Squill Prepared from the bulb of the sea onion, squill is one of the oldest medicinal agents. The earliest reference to it is found in a prescription contained in the Ebers papyrus, about 1500 B.C. For a long time it fell into disuse, apparently because of its tendency to cause nausea and vomiting. It enjoyed renewed waves of popularity, first in the middle of the eighteenth century, largely through the writings of van Swieten, and again, in the past 15 years, as a result of the isolation of various so-called "active principles." Most of these, however, have been only a little purer than the crude extracts, and because of their poor absorption from the

gastrointestinal tract they have rightly been regarded as undesirable substitutes for digitalis

Recently, by modifying the methods of extraction, a new preparation of squill has been made and is now marketed under the trade name, "Urginin." It is a mixture, in approximately equal proportions, of two of the active, water-insoluble glucosides—crystalline scillonin A and amorphous scillonin B. For oral use, it is put up in tablets containing 0.5 mg. each.

A clinical study of urginin was made during the past year in our department at the Presbyterian Hospital, by Chamberlain and Levy.⁵ It was found that, in patients with cardiac insufficiency, urginin exerted an action on the heart like that of digitalis. The effects were noted in the presence of regular rhythm as well as when the auricles were fibrillating. The therapeutic potency of urginin, in terms of cat units, was about one-half that of digitalis. Thus, approximately two cat units of urginin were required to induce effects, both therapeutic and toxic, comparable to those induced by one cat unit of digitalis. This difference in activity may be ascribed to less complete absorption or more rapid elimination in the case of urginin.

A satisfactory scheme of dosage, when no digitalis or urginin has been given for at least ten days preceding, was 1.5 mg. (3 tablets) three times a day after meals for two days, 1.0 mg. (2 tablets) twice daily until the desired effects were produced. The daily maintenance dose ranged from 0.5 to 2.0 mg., the average was 1.0 mg. (2 tablets).

Toxic effects noted were nausea, vomiting, diarrhea, transient auricular fibrillation, auriculoventricular nodal rhythm and varying degrees of heart block. But every patient without previous nausea was able to retain urginin if given after a meal in amounts not exceeding 1.5 mg. (3 tablets). Premature beats as evidence of intoxication were not observed.

The effects on the electrocardiogram were similar to those seen after digitalis.

It was concluded that urginin is an effective cardiac remedy. It offers no advantages over digitalis with respect to its action in myocardial insufficiency. But it serves a purpose in that occasionally, patients in whom digitalis induces nausea, vomiting or diarrhea, are able to take urginin without suffering from unpleasant symptoms. It may be useful also when a patient harbors an unfounded prejudice against the use of digitalis.

Strophanthus Because of the variability with which *strophanthus* is absorbed from the gastrointestinal tract, it is unsuitable for oral administration. Crystalline *strophanthus* (ouabain), derived from the seeds of *Strophanthus gratus*, is particularly useful for intravenous injection, because its crystalline character and known chemical composition make accurate dosage possible. An initial effect is apparent in from 5 to 20 minutes, the maximum effect in from 15 to 50 minutes.³⁸ If given in fractional doses, it may be administered safely to patients with auricular fibrillation with rapidly beating ventricles, who have not received digitalis within a week.

In them, ventricular rate can be used as a guide of effect. Greater care is necessary when it is given in the presence of regular sinus rhythm, when clinical improvement is the only criterion of full therapeutic effect. In those occasional instances when rapid action seems necessary, 0.5 mg. may be injected at the first dose, to be followed at intervals of one hour or more by 0.1 or 0.2 mg., up to a total dose of 1.0 mg. Treatment may then be continued by the use of digitalis, given by mouth, by rectum or by intramuscular injection.

Amorphous strophanthin, obtained from *Strophanthus kombé* or *hispidus*, is less uniform in composition and is not superior to the various aqueous preparations of digitalis.

Diuretics (a) *The xanthine group*. Often rest in bed, curtailment of fluid and salt intake and the exhibition of digitalis promote diuresis and relieve edema. If, after these measures have been tried, there is evidence of continued retention of fluid in the tissues, diuretic drugs are indicated.¹⁶ For use by mouth a member of the xanthine group may be given.²⁵ Theobromine sodium-salicylate (diuretin) is one of the most valuable because of its relatively slight toxicity. It may be taken in powder or tablet form, in doses of 1.0 gm. (15 gr.), three or four times a day for two or three days, and then repeated at intervals of several days. Theophylline (theocin) may be similarly used in doses of 0.2 gm. (3 gr.) three or four times a day, but is more likely to upset the digestion. Theobromine-calcium salicylate (theocalcin) is a third member of the series, to be given in doses of 1.0 gm. (15 gr.) three or four times a day.⁴⁰ Theocalcin, being well tolerated, is of particular value when it is desired to maintain mild diuresis over a period of days or weeks.

(b) *The mercurials*. Mercupurin and salyrgan have largely supplanted the xanthines.^{8, 9, 33} They are more rapid in action and more potent, yet relatively non-toxic. Renal irritation is rarely observed. They are given preferably by intravenous injection, in doses of 1 to 3 cc., the smaller amount being injected first to test the patient for possible idiosyncrasy to mercury. The injection may be repeated at intervals of four to six days when required. Mercupurin, which is a combination of theophylline with mercury, is less irritating to the tissues than salyrgan and can be given intramuscularly, if necessary. Both preparations are available in the form of suppositories,* they are somewhat less effective when given by rectum. The action of the mercurials may be enhanced by administering ammonium chloride or ammonium nitrate for from 24 to 48 hours prior to using the diuretic. These "acid producing" salts are best tolerated in the form of enteric coated pills of 0.5 gm. (7½ gr.) each. As much as 8 to 10 gm. of one or the other must be given in 24 hours, in divided doses, to be effective.¹⁷ Usually mercury alone is adequate, the tendency for the am-

* In the case of mercupurin, the suppositories do not contain theophylline and are known as "mercurin."

monium compounds to cause nausea and vomiting when taken in such large amounts, limits their clinical usefulness

The xanthines, according to the best evidence, increase glomerular filtration, the mercurials diminish tubular reabsorption. Since these two groups of substances thus differ in their mode of action, they may sometimes be used alternately to advantage

Sedatives The late Sir James Mackenzie has wisely said that "little benefit is likely to arise from treatment so long as a patient is worried or sleepless." The cardiac patient who has tossed about, harassed by dyspnea, awakens from a sound sleep refreshed and encouraged, after a hypodermic injection of 15 mg ($\frac{1}{4}$ gr) of morphine sulphate or 20 mg ($\frac{1}{3}$ gr) of pantopon. This may be repeated for several nights, or even during the day, until other measures have so improved the circulation that milder sedatives will serve, or none are required. One of the barbituric acid derivatives, such as phenobarbital, or a bromide mixture, given three or four times daily, will often allay restlessness. For insomnia, a barbiturate, such as sodium amytal or nembutal, will assure comfortable nights. A tranquil frame of mind is essential for proper relaxation and cooperation.

Cathartics Vigorous purging, with evacuation of copious watery stools, is no longer regarded as good practice. Fluid can be eliminated more readily and with less discomfort through the kidneys. The frequent use of bedpan or commode is tiring and requires effort at a time when rest is of first importance. Mild daily catharsis to prevent clogging of the intestinal tract is desirable. At the start, a dose of magnesium sulphate or compound jalap powder rids the bowel of accumulated waste, later, milder cathartics, such as cascara, are effectual, aided, if necessary, by a small, bland enema.

Glucose The intravenous injection of hypertonic glucose solution has been recommended, particularly by European authors. Sometimes it appears to help in initiating improvement when other measures have failed. The sugar is a nutrient for the myocardium, exerts a diuretic action and sometimes aids in relieving frequent paroxysms of dyspnea. From 50 to 100 cc of a 50 per cent solution are injected once or twice daily for several days.

Oxygen By definition, a drug is any substance used medicinally. Though administered by inhalation a gas falls into this category. Myocardial insufficiency is often accompanied by a state of marked anoxemia, this can be relieved by increasing the oxygen content of the inspired air to 50 per cent or more.¹ There result elevation of the oxygen saturation of the blood to normal, decrease in pulmonary ventilation and increase in the carbon dioxide concentration of the expired air. The heart rate becomes slower, dyspnea is relieved, cyanosis disappears, as does Cheyne-Stokes respiration, if present. The patient is less restless and within 24 hours may be able to sleep without the aid of narcotics. Part of the burden of a failing heart is lightened. In cases of chronic failure, not yielding to other forms of

therapy, residence in an oxygen tent or chamber over a period of days, or even weeks, has occasionally served to promote diuresis and by so doing, has started a chain of events leading to the recovery of compensation.

Patients with active rheumatic carditis, in our experience, have not responded favorably. Those in whom failure was due to coronary heart disease or hypertension have done well. Prolonged residence in an oxygen chamber has also been found useful in preparing persons with cardiac insufficiency for operative procedures. Cases of hyperthyroidism have been conspicuous in this group. The technic of oxygen therapy need not be given in detail here. The tent is now a familiar apparatus and is quite generally available. For prolonged periods, the chamber is more comfortable, though expensive to install and operate. The nasal catheter may be employed as a measure of moderate effectiveness. The mask recently described by Barach is still undergoing trial.

CARDIAC PAIN

Paroxysmal pain in the chest may be due to a variety of causes. Upon precise definition of etiology will depend the form of therapy. These remarks will be confined to a consideration of the discomfort commonly referred to as anginal, and due, in most instances, to atherosclerosis of the coronary arteries.

The Nitrites An attack will usually subside within a few minutes on the cessation of activity or the passing of an emotional upset. Judicious use of one of the nitrites affords prompt symptomatic relief, due to reduction in systemic arterial pressure as well as to dilatation of the coronary arteries. Nitroglycerine is convenient because it can be carried as a tablet, which should be thoroughly chewed before swallowing. A small dose, 0.3 to 0.4 mg ($\frac{1}{200}$ to $\frac{1}{150}$ gr.) often suffices and may not cause the flushing and headache sometimes so annoying after the larger and more commonly used tablet of 0.6 mg ($\frac{1}{100}$ gr.). There are cases in which only the larger dose is effective. It is important to insist that nitroglycerine tablets be fresh, after they have been exposed to the air for six to eight weeks, their strength deteriorates. The odor of amyl nitrite, in the form of pearls, has made it less popular than the nitroglycerine tablet. When an attack persists for more than an hour and is not relieved by nitrite, particularly if this is contrary to previous experience, occlusion of a coronary branch should be suspected.

The value of nitroglycerine as a prophylactic, suggested by the Englishman, Leech, in 1893, is not sufficiently appreciated. It was first called to my attention by Professor K. F. Wenckebach, of Vienna, a number of years ago. If a tablet or, if necessary two, be taken prior to anticipated effort or nervous strain, the activity can often be carried through to a painless conclusion. There is no harm in repeating the dose several times during the day. I have seen patients who have taken from 15 to 20 tablets of nitroglycerine daily over a period of years, without apparent harm and with no

loss in effectiveness. In my hands, the routine use of the nitrites, given at regular intervals during the day, has not proved as successful as when necessity or prevention served as indications.

The continued administration of those nitrites having a more prolonged action sometimes leads to marked lowering of blood pressure and syncope. If nocturnal attacks are troublesome, erythrol-tetranitrate, 30 mg ($\frac{1}{2}$ gr) may be taken immediately before retiring, the effect lasts for four or five hours and sometimes makes undisturbed sleep possible.

Sedatives The patient subject to anginal attacks is apprehensive. Mild sedatives produce a more equable state of mind and lower the threshold for pain. Phenobarbital, 15 to 30 mg ($\frac{1}{4}$ to $\frac{1}{2}$ gr) or a mixture containing 0.6 to 1.0 gm (10 to 15 gr) of bromide serves well in this capacity, and may be continued intermittently or continuously for weeks or months.

The Xanthines as Coronary Dilators Derivatives of theophylline and theobromine enjoy wide popularity for prolonged, daily administration. They are prescribed in the belief that they cause dilatation of the coronary arteries, prevent spasmodic contractions of these vessels and augment the flow of blood through the myocardium. There is at present disagreement as to their value, based both on laboratory and clinical studies. Smith and his collaborators, working with theophylline-ethylenediamine (aminophyllin) have found that in normal dogs, after ligation of a coronary artery the size of the infarct produced was smaller when the drug was given than in controls.¹² Gold and his co-workers¹⁵ were unable to confirm these results in cats. Wiggers and Green,³¹ using a different technic, concluded that "an increase in collateral circulation sufficient to be of functional use cannot be attained by use of vasodilating drugs after complete coronary occlusion." Whether these observations are applicable to the diseased human heart has not been demonstrated.

After administering members of this group of drugs to patients, and using adequate controls, different clinicians have reached opposite conclusions. Some, including Evans and Hoyle,¹⁰ and Gold, Kwit and Otto,¹¹ have stated that the xanthines exert no specific action which is useful in the routine treatment of cardiac pain. Others have been impressed by the favorable results. In a recent study, Brown and Riseman³ have determined the comparative value of eleven preparations, as judged by the usual clinical criteria, and also by measuring the amount of work, under standardized conditions, which could be done before the appearance of cardiac pain. They found that not all patients respond favorably to purines, but they offer no method of distinguishing between those who do and those who do not. Each preparation was given four times daily—on arising, after lunch and supper, and at bedtime. The order of effectiveness and the individual doses were: theophylline with sodium acetate, 0.25 gm (4 gr), theobromine with sodium acetate, 0.5 gm (7½ gr), theophylline with calcium salicylate 0.5 gm (7½ gr), theophylline with ethylenediamine 0.2 gm (3 gr).

The number and intensity of attacks of anginal pain are subject to wide variations, over a period of months or years, in the same person. Rest, adaptation to limitations, and acquisition of emotional stability often result in great symptomatic improvement in a relatively short time. Appraisal of the therapeutic result based upon the patient's own account is subject to error, the standardized exercise tolerance test, though partially objective, likewise depends for its end-point upon the sensations of the individual tested. In the light of such conflicting evidence, final judgment as to the virtues of the xanthines must be deferred. It is indeed questionable whether they accomplish any good.

Organ and Tissue Extracts A number of these have been tried, both by mouth and by hypodermic injection. I have never observed any benefit from their use.

ACUTE CORONARY OCCLUSION

Abiupt closure of a coronary branch, in its early stages, is a medical emergency. Complete rest and relief of pain by generous doses of morphine are the immediate requirements. It is now generally accepted that digitalis, in the absence of signs of cardiac insufficiency, should not be given. If congestive failure develops, or the attack is accompanied by the onset of auricular fibrillation or flutter, with rapid ventricular rate, it must be used in effective amounts, but cautiously. Digitalis is a cardiac stimulant, causing increased force of muscular contraction, the heart which is the site of recent infarction needs rest. The danger of causing rupture of the ventricle by the use of digitalis has been over-emphasized, but the possibility of inducing ventricular fibrillation is real, particularly after the acute phase has passed and the stage of repair is in progress^{2,13}.

If pain is severe or the signs of anoxemia are manifest, administration of oxygen, in concentration of 50 per cent, preferably in a tent, is indicated. Discomfort is lessened and the failing heart is often tided over a critical period. As pointed out by Levy and Barach²² in 1930, "in certain instances, effective use of oxygen may be responsible for the saving of life."

For collapse, caffeine sodium-benzoate, in doses of 0.3 to 0.5 gm (5 to 7½ gr), may be injected into a vein. Should nourishment be poorly taken or vomiting persist, hypertonic glucose solution, 50 per cent, is sometimes helpful. From 50 to 100 cc are given intravenously once or twice daily for several days.

The treatment of various cardiac irregularities which may occur as complications is considered in the following section.

CARDIAC ARRHYTHMIAS

Auricular Fibrillation In this form of irregularity, in which a circus movement travels an irregular course about the mouths of the great veins, the ventricles usually beat rapidly. Fibrillation of the auricles may be

paroxysmal or permanent. As a rule, it occurs in a diseased heart, most frequently in association with mitral stenosis, under these conditions, it is an expression of myocardial insufficiency and auricular dilatation. Occasionally it is observed in the absence of organic cardiac disease, due to toxic influences or neurogenic disturbances. No matter what the etiology, the first aim of treatment is to slow the ventricular rate. For this purpose, digitalis in full doses is dramatically effective, particularly in rheumatic and coronary heart disease. In cases with toxemia due to bacterial poisons, and in hyperthyroidism, slowing of rate is relatively slight.

When fibrillation is of recent onset, administration of digitalis may be followed by resumption of regular sinus rhythm, due to betterment in cardiac function. Should fibrillation persist, the rate should be brought to a level ranging between 70 and 80, at rest, and held there by proper adjustment of a daily maintenance ration. Patients with permanent auricular fibrillation, in whom the heart rate, undigitalized, is above 80, must take digitalis for the balance of their lives.

In certain cases, normal rhythm can be restored by the use of quinidine.⁴ Accumulated experience has shown that the number suitable for the use of this drug is limited. There are dangers from its administration.²⁰ Such discomforts as tinnitus, nausea, vomiting or diarrhea, though unpleasant, are of minor import. But induction of heart failure, syncope, collapse, embolic phenomena and sudden death are untoward effects which must be considered whenever quinidine is given. The careful selection of suitable subjects minimizes the hazards. Unfavorable criteria are idiosyncrasy to cinchona derivatives, fibrillation of long standing, cardiac enlargement, mitral stenosis, active carditis, cardiac insufficiency, previous occurrence of emboli to lungs or systemic arteries, complete heart block, bundle branch block, hyperthyroidism. It is at once apparent that only a small group is left. Indications favoring its use are fibrillation of recent onset, absence of cardiac enlargement, no valvular disease, fibrillation persisting after subtotal thyroidectomy for hyperthyroidism.

Most patients with organic heart disease and auricular fibrillation of long standing (longer than six months) are not greatly improved by restoration of normal rhythm. There is always the possibility, and indeed, the likelihood, that the irregularity will recur, with the sudden onset of a rapid ventricular rate. This requires another period of rest and quinidine therapy. With continuous digitalis dosage, the heart is stabilized and the rate is controlled. The possibility of the occurrence of upsetting episodes at inopportune moments is eliminated. Occasionally, however, when all the usual measures have proved unavailing in combating failure, restoration of normal rhythm may serve to turn the tide, in these rare instances, quinidine may be given a trial.

Before giving quinidine, congestive failure, if present, should be controlled by digitalis, and the ventricular rate should be retarded. The treatment should be carried out with the patient in bed, under careful observation,

preferably with electrocardiographic control. This form of therapy is not recommended for ambulatory cases.

A satisfactory scheme of treatment is as follows, the individual doses being given, by mouth, at intervals of two hours. *First day*, two doses of 0.2 gm (3 gr) each, these are to test for a possible idiosyncrasy to cinchona. Normal rhythm may occasionally ensue from this small, preliminary dosage. *Second day*, three doses of 0.4 gm (6 gr). *Third day*, four doses of 0.4 gm. *Fourth and succeeding days*, five doses of 0.4 gm. Larger amounts have been used but are not without added risk. The treatment may be continued for a week, though usually, a successful result, if obtainable, is accomplished in from four to six days. If it is necessary to prolong treatment beyond this period, normal rhythm, even though restored, is often not maintained. In a few cases, six to eight doses in a day have succeeded when five have failed. Intravenous injection of quinidine is inadvisable, several fatalities have followed this procedure.

After restoration of normal rhythm, it is desirable to continue with small doses of 0.2 gm (3 gr) three times daily, for several weeks. These tend to prevent relapse. Such amounts, or even larger doses, if necessary (0.4 gm three or four times daily), may be taken for weeks or months without harm or discomfort. A similar plan may be followed, often with conspicuous success, in cases of paroxysmal auricular fibrillation to prevent the onset of attacks. If these recur at frequent intervals, it is best to encourage permanent fibrillation and to control ventricular rate with digitalis.

Auricular Flutter. This is treated with digitalis in the same manner as described for fibrillation. Usually, full dosage is followed by the onset of fibrillation, with subsequent transition to normal rhythm. If flutter persists, quinidine may be tried, but the results, as a rule, are better with the foxglove. Should flutter be converted to fibrillation and normal rhythm not be resumed, quinidine may be used with good effect. There are occasional instances of flutter which are resistant to drug therapy. If the ventricular rate is controlled by digitalis, the patients are able to carry on their usual activities, provided the myocardium is functionally adequate. In several such cases, normal rhythm has been resumed spontaneously, for no apparent reason, after the lapse of months or years.

Paroxysmal Tachycardia. If the attacks are short and infrequent, no treatment is necessary. For the longer paroxysms, recurring at short intervals, simple measures should be tried, such as carotid or ocular pressure, change in posture, the induction of vomiting or forced respiration. Should these prove unsuccessful in terminating the bout, acetyl-B-methylcholine (mecholyl) may be injected hypodermically, in a dose of 20 to 40 mg. It is a powerful stimulant of the parasympathetic nerves. Starr,²⁸ who has written extensively concerning its use, has had excellent results, and these we have been able to confirm. The attack usually ceases in from one to twelve minutes. Unpleasant symptoms are common, these are dyspnea, substernal pain, vomiting, sweating, flushing and salivation. Atropine, 1/2

mg given intravenously, will counteract the action of acetyl-B-methylcholine almost immediately, and may be given if the reaction is severe. Attacks of auricular or supraventricular origin are usually stopped by the drug alone. If this is insufficient, carotid pressure during the drug's action is sometimes successful. It is not a dangerous remedy, but it should be used with caution in patients with asthma and in those suffering from conditions responding to epinephrine, which is a physiological antagonist of the choline.

Quinidine, given by mouth, is occasionally effectual in bringing about reversion to normal rhythm, particularly when the arrhythmia is of the ventricular type¹⁸. In rare cases an attack is terminated by the intravenous injection of strophanthin. Digitalis or strophanthin must not be given if the tachycardia is of ventricular origin, because of the danger of inducing ventricular fibrillation.

Syrup of ipecac, 8 to 16 c.c. (2 to 4 teaspoonfuls), may be taken orally to induce nausea or vomiting. This is an unpleasant measure, but, by reflex vagal stimulation, it sometimes terminates an attack.

The prevention of paroxysms by drugs is uncertain. Quinidine, in small doses (0.2 gm. three or four times a day) is the most valuable remedy and may be continued, if effective, for an indefinite time. Digitalization, with subsequent daily maintenance rationing, may likewise be tried. Sedatives, in cases in which nervous influences play a part in precipitating attacks, lessen discomfort and lower the threshold for disturbing factors.

Complete Heart Block Permanent heart block, unless accompanied by heart failure, rarely requires treatment. In certain instances, ventricular standstill or paroxysms of ventricular fibrillation cause dizziness, syncope or convulsive seizures (Stokes-Adams syndrome). It is necessary to know which mechanism is responsible for these attacks in order to carry out appropriate therapy. When ventricular asystole occurs frequently and is of sufficiently long duration to produce the symptoms of cerebral anemia, epinephrine is the best preventive¹¹. It is given in doses of 0.5 to 1 c.c. (8 to 15 minims) of the 1:1000 solution, by subcutaneous or intramuscular injection. The dose may be repeated as often as every two hours, if necessary. On rare occasions, if ventricular standstill is prolonged, intracardiac injection of epinephrine may save life. When the attacks are due to ventricular fibrillation, epinephrine is contraindicated, for it may perpetuate the mechanism and cause death.

If ventricular standstill tends to recur, ephedrine sulphate is sometimes partially or wholly effective as a prophylactic³⁷. Its action is similar to that of epinephrine, but is of longer duration. Ephedrine is given by mouth, in doses of 30 mg. ($\frac{1}{2}$ gr.) three or four times a day. Barium chloride, because it increases the irritability of the ventricles, and so lessens the likelihood of standstill, has been employed successfully in a few cases⁹; in patients under my observation, it has been less effective than ephedrine.

It may be given by mouth in doses of 30 mg ($\frac{1}{2}$ gr) three or four times a day

In the presence of heart block, quinidine should not be given, since there is some evidence that disturbances in the conduction system favor the development of ventricular fibrillation

MISCELLANEOUS CONDITIONS

In *diabetes mellitus*, coronary sclerosis is frequently present. Insulin both by causing hypoglycemia and by sympathetic stimulation, places an added burden of work upon the heart and sometimes induces paroxysms of anginal pain. In elderly diabetics, therefore, insulin should be given with caution, it may cause acute coronary insufficiency and sudden death. It is wiser, in many of these patients, to attempt to control hyperglycemia by dietary measures, even though the urine shows a faint reducing reaction and the level of the blood sugar is somewhat elevated³²

The facts concerning the value of intensive anti-luetic therapy in *aortic syphilis* are not yet fully known²⁶⁻²⁷. It is well to keep in mind two points: first, the cardiologist must have cognizance of the specific nature of the lesions in the heart, second, the syphilologist must appreciate the limitations placed upon anti-luetic treatment by the cardiac disability. As Wile³⁵ has phrased it in his "therapeutic paradox": "the patient gets well or better of his syphilis, but may die as the result of the dispersion of his syphilitic cardiac lesion". Particularly when involvement of the orifices of the coronary arteries is suspected, the arsenical preparations must be given with great caution, in the judgment of many, it is best, under these circumstances, not to use them at all²¹. Bismuth, mercury and iodide usually can be given with safety.

The use of digitalis in *lobar pneumonia* has occasioned wide differences of opinion. Some have stated that to employ it is dangerous and actually does harm. Others have maintained that every patient with pneumonia should receive it. As a matter of fact, circulatory weakness in pneumonia is not primarily of cardiac origin, the routine use of digitalis, therefore, is not sound practice. The situation was summed up by Cohn in 1935, after a critical analytical study⁷. He concluded that giving digitalis does not seem to influence the course of events in uncomplicated lobar pneumonia. But when congestive failure appears, as it may in patients with cardiac disease, or when auricular fibrillation or flutter occurs, the action of digitalis appears to be beneficial. Under these circumstances, it is sometimes life-saving. The outcome in lobar pneumonia, however, depends primarily upon the severity of the disease itself, and this is determined by the presence of bacteremia, the number of lobes involved, and the existence of complications.

CONCLUSION

It is apparent, even from this incomplete discussion, that there are indeed many remedies which can be applied, under different circumstances, in disorders of the heart. Precisely when to prescribe each drug, how much to give, and when to stop, are matters of vital importance. Judgment, based on close observation and experience, is sometimes difficult. Because of the large number of variable factors which modify the picture of disease in human beings, it is not possible to carry out treatment according to a fixed formula. An attempt has been made to describe some of the medicinal tools which have been found useful, and to indicate certain ways in which they may be employed with benefit. Upon the skill of the medical workman will depend, in large measure, the successful outcome of his therapeutic efforts.

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THE USE OF THE MERCURIAL SUPPOSITORY AS A DIURETIC ¹

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INTRODUCTION

ORGANIC mercurial compounds have been recognized as having valuable diuretic properties since 1920 ¹ and have been used with increasing frequency since the introduction of salyrgan in 1924 ² Later mercupurin (novurit), neptal and mercurosol were used These drugs proved to be of great benefit in the treatment of cardiac edema, of moderate assistance in the management of nephrotic edema, and of lesser therapeutic value in the edema and ascites of hepatic cirrhosis In addition to the known limitations, the drugs were objectionable because they were mercurials and thus renal irritants Great care was therefore necessary in controlling their administration to avoid kidney damage They were effective only when given intravenously or intramuscularly which entailed some discomfort, and occasionally slough or venous thrombosis as a complication

In an effort to avoid these latter difficulties, salyrgan has been administered orally, but with poor results ³ In 1931, Engel and Epstein used salyrgan rectally in 100 cc of water with fair results ⁴ More recently, rectal suppositories containing 0.5 gm of novurit † were made available abroad The active principle was a sodium salt of an organic mercurial combined with theophylline ⁵ In this country similar (mercurin) suppositories have been offered containing 0.5 gm of the organic salt found in mercupurin, without theophylline Even more recently salyrgan suppositories containing theophylline have become available Clinical investigators were immediately interested in the efficiency of these preparations

Parkinson and Thomson ⁵ made a study of novurit suppository, novurit and salyrgan (each with and without ammonium chloride) They concluded that "novurit suppository is an effective and safe diuretic" and that all three agents are more effective after the administration of ammonium chloride In the 10 cases reported they avoided the use of digitalis during their determinations Fulton ⁶ made a similar study using mercurin suppository, mercupurin and salyrgan on 25 cases and reported favorable results with mercurin suppositories Herrmann and Decherd ⁷ published some studies on diuretics including the satisfactory use of mercurin suppositories

* Received for publication December 20, 1937

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† Campbell Products, Inc, manufacturers of mercupurin and mercurin suppositories in this country, assure us that their products are identical with novurit and novurit suppositories According to their statement, the term "novurit suppository" is misleading because the suppositories contain no theophylline

METHOD AND SELECTION OF CASES

On the wards at New York Post-Graduate Hospital mercurin suppositories have been used on one or more occasions in 12 cases of edema. Of these 12 cases, the edema was due to congestive heart failure in 10, while cirrhosis of the liver was considered to be the causative factor in the other two. In the 10 cases of cardiac decompensation the mercurin suppositories were used in conjunction with the routine treatment of bed rest, sedation, digitalis and ammonium chloride. In three of the cases intravenous mercurials were employed also, and a comparison of the effectiveness of the parenteral and rectal route is available.

In the two cases of cirrhosis of the liver mercurial diuretics were administered by both the above routes, in one case, both before and after ammonium chloride ingestion.

These cases are briefly reported below. The therapy used is indicated by the routine just mentioned and is apparent in the table and figures. The only details included below are those directly relating to the problem, namely, whether mercurial suppositories are an aid in the treatment of edema.

EXPERIMENTAL OBSERVATIONS AND DISCUSSION

Case 1 (Table 1) A. B., female, aged 44, was admitted complaining of swelling of abdomen and legs, and "weakness around her heart" for the preceding two weeks. She had been short of breath for two months. Her illness began two years previously with fever, swelling of the joints and "heart trouble." Physical examination revealed a slight degree of dyspnea and orthopnea. Moist râles were present in the bases of both lungs. Her heart was moderately enlarged to the left. A shock and systolic thrill were felt at the apex. A systolic murmur was heard at the apex, the pulmonary second sound was slightly accentuated. The heart rate varied from 96 to 108 per minute and was totally irregular. Blood pressure was 136 systolic and 82 diastolic. The abdomen was moderately distended, with signs of free fluid. The lower extremities showed edema grade one plus.

Case 2 (Table 1) H. I., male, aged 47, was admitted because of shortness of breath and swelling of the abdomen. As a young man (25 years before) he had had rheumatic joint and heart disease and had been given salicylates. He had been entirely well until the week before examination when he noted the above symptoms which became progressively worse. He was unable to sleep at night because of shortness of breath and coughing spells. Although no chest pain was present the patient complained of a pounding heart. Physical examination revealed the patient to be dyspneic and orthopneic. The teeth were carious and infected. The chest was dull over both bases, râles were present, and breath sounds slightly decreased. The heart was somewhat enlarged. There was a systolic murmur at the apex and the pulmonic second sound was accentuated. The apex rate was 126, radial rate 80 with total irregularity, blood pressure 160 systolic and 100 diastolic. The abdomen was obese. The liver was palpated down to the umbilicus and found to be firm and tender. The spleen was not palpated and no ascites was apparent. Ankle edema was absent.

A mercurin suppository was given on the second day but no diuresis was apparent until three days later after ammonium chloride gr 120 had been given daily.

TABLE I
The Effect of Mercurin Suppositories on the Volume Output of Urine in Cases of
Cardiac Decompensation and Cirrhosis of the Liver

	Day of Observation	Water Balance		Ammonium Chloride	Digitalis	Mercurin Suppository		Remarks
		24 hr Intake c c	24 hr Output c c			Grains	Time	
Case 1 44, F Rheumatic heart disease, inactive	3	500	600	45	1 $\frac{1}{2}$			
	4	1280	3350	60	1 $\frac{1}{2}$		10 00 a m	
	5	900	1750	45	1 $\frac{1}{2}$			
	6	800	1800	60	1 $\frac{1}{2}$		10 00 p m	
	7	1000	2150	60	1 $\frac{1}{2}$			
Case 2 47, M Rheumatic heart disease, inactive	2	1600	1100	120	6		1 15 p m	
	3	1550	950	120	1 $\frac{1}{2}$			
	4	1600	2150	120	1 $\frac{1}{2}$			
	5	1610	1525	120	1 $\frac{1}{2}$			
	6	1430	1680		1 $\frac{1}{2}$			
Case 4 51, F Hypertensive cardiovascular disease, obesity, coronary occlusion	26	1050	525		1 $\frac{1}{2}$			
	27	1200	2575	90	3		10 00 a m	
	28	1550	750	135	1 $\frac{1}{2}$			
	29	1450	1200	135	3			
	34	1150	790	135	1 $\frac{1}{2}$			
	35	950	970	135	3			CO ₂ 49.4 Volumes per cent
	36	650	500	135	1 $\frac{1}{2}$			
	41	1080	920	135	1 $\frac{1}{2}$			
	42	1500	2150	135	3		9 00 a m	CO ₂ 52.2 Volumes per cent
	43	1140	735	135	1 $\frac{1}{2}$			
Case 10 44, M Rheumatic heart disease, active, chronic glomerular nephritis, embolism of cerebral vessel	2	1420	1050		3			
	3	1330	1020		3		11 30 a m	
	4	1205	1070		3			
	5	1480	1275	120	3			
	6	1350	1400	120	3			
	7	1480	870	120	3			
	8	1230	950	120			9 00 a m	
	9	1650	1300	120				
	10	1690	1350	120				
	11	930	440					
Case 11 33, M Syphilis, jaundice, ascites	30	1150	1050					
	31	2650	1295				7 00 a m	
	32	1300	1750					
	33	1375	1230					
	34	1200	2050	90				
	35	3700	2370	90				
	36	1255	1100	90				
	37	1050	2350	90			1 00 p m	Expelled after 20 min
	38	1340	2200	90			10 30 a m	Expelled after 20 min
	39	1300	3050	90				Mercupurin 2 c c intravenously
Case 12 58, M Arteriosclerotic heart disease, portal cirrhosis	4	1750	850		3		8 30 a m	
	8	1380	820		3		8 30 a m	
	12	1290	975		3		8 30 a m	
	21	1550	600				5 00 p m	
	32	1620	2050					Mercupurin 2 c c intravenously 8 30 a m Mercupurin 2 c c intravenously 8 30 a m

Case 3 (Figure 1) M M, female, aged 44, was admitted complaining of shortness of breath, swelling of feet and ankles and of some pain in the abdomen. Three years before the patient first began having asthmatic attacks at night. The attacks were severe and the patient was obliged to sit up to get her breath. Her feet and ankles had been swollen at times for ten months. This was her second admission within six months. She had been receiving digitalis in the clinic. She had precipitated her present cardiac decompensation by over-exertion.

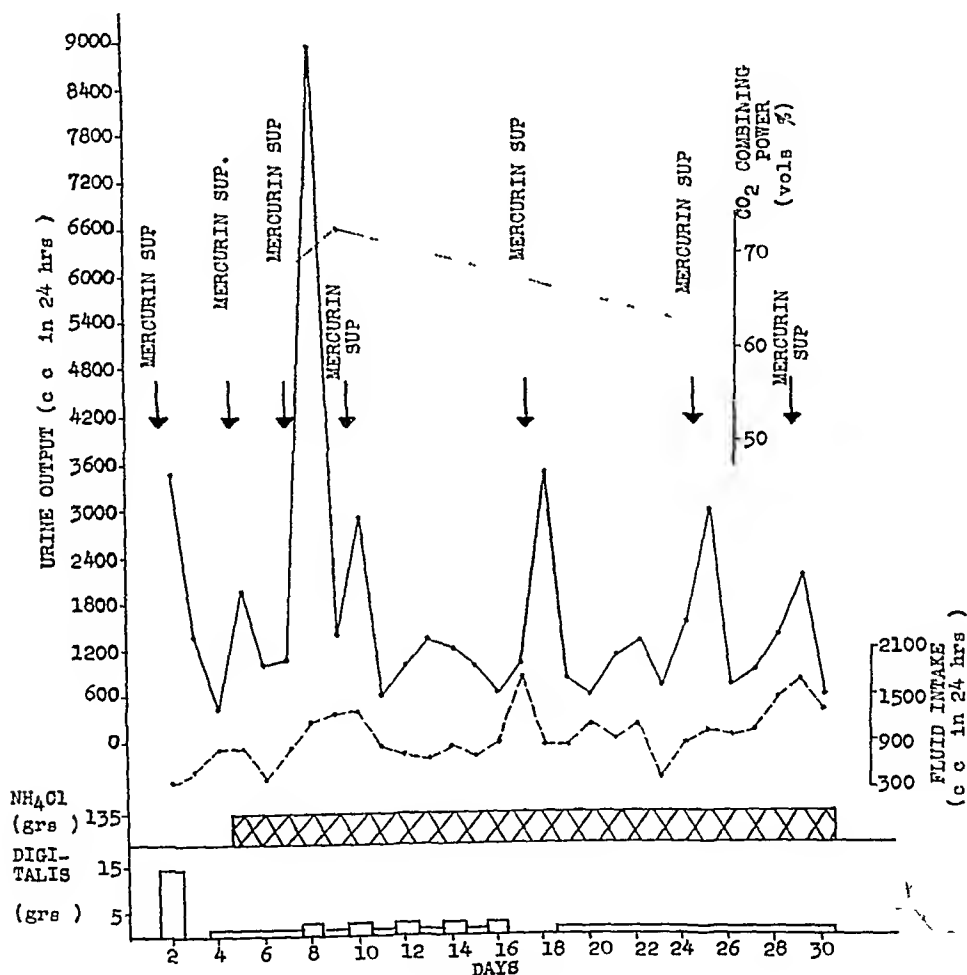


FIG 1 *Case 3* Aged 44, F Hypertensive cardiovascular disease

Physical examination revealed marked dyspnea, edema and ascites. Her chest was dull on the right to the spine of the scapula. Râles were heard over both bases with decreased fremitus in the right base. The heart was enlarged to the left, a systolic blow was heard at the apex, auricular fibrillation was present with a rate of 92, the blood pressure was 190 systolic and 110 diastolic. The abdomen was greatly distended with fluid. The liver edge was tender and extended 8 cm below the costal margin. The spleen was not palpated. The legs were edematous to a maximum degree. A pustular eruption on an erythematous base was observed on both thighs.

A graphic presentation of this case (figure 1) shows that on her second day in bed, in response to increased digitalis, bed rest and a mercurin suppository, she had an output of 3,475 c c of urine. She had marked anasarca, cyanosis and dyspnea. On the fifth day her condition seemed more critical than on admission. Ammonium chloride gr 135 daily was begun and another suppository used, with a resultant urinary output of only 1,950 c c. However, on the fourth day of ammonium chloride, another mercurin suppository was followed by a diuresis of 8,750 c c. The ammonium chloride was continued and a mercurin suppository used on four subsequent occasions during the next three weeks and in each instance the output exceeded that of the fifth day. This patient on admission and for the first eight days in the hospital was so decompensated that one would expect all of her excretory mechanisms to be impaired sufficiently to induce an acidosis, however, on the second day of hospitalization the CO_2 combining power was 58.9 volumes per cent and on the ninth day after receiving ammonium chloride gr 135 daily for four days (the morning after the greatest urinary output) the CO_2 combining power was 73 volumes per cent (done in duplicate). Thirteen days later with continued ammonium chloride therapy, the CO_2 combining power was 63.3 volumes per cent and the increased urinary output was maintained.

Case 4 (Table 1) O. R., female, aged 51, was admitted for the second time within seven months complaining of shortness of breath, cough, blueness of the face after coughing, pain over the heart and swelling of the ankles. Upon physical examination the patient was found to be markedly obese (weight 233 lbs.), slightly cyanotic, and orthopneic. The chest was dull on percussion over both bases and moist rales were present. The heart was enlarged to the left. The pulse rate was 120, blood pressure 160 systolic and 100 diastolic. The abdomen was extremely obese. Ankle edema was graded one plus.

This patient received ammonium chloride gr 135 daily beginning the twenty-seventh day of hospitalization. After eight days of ammonium chloride medication the CO_2 combining power was 49.2 volumes per cent and after 16 days it was 52.2 volumes per cent. A mercurin suppository resulted in a marked diuresis on this day.

Case 5 (Figure 2) T. M., male, aged 51, had nocturnal cough for several months and these "asthmatic attacks" had been increasing in severity. For the past month he had been forced to use three pillows and was very short of breath upon the slightest exertion. He was conscious of his heart pounding with an occasional pronounced thump. His legs had been swelling for about six weeks. For the past two weeks he had had a sense of fullness in his upper abdomen which was most distressing. The patient was observed to be orthopneic and dyspneic. He had dullness and rales over both bases. His heart was enlarged to the left and was totally irregular in rhythm. There were no murmurs. The apical rate was 114 and the blood pressure 146 systolic and 76 diastolic. His liver was enlarged downward and tender. Sacral and ankle edema were graded three plus.

This patient received 1 c c of salyrgan intravenously on the first day which resulted in a very mild diuretic response (figure 2). After digitalis

and ammonium chloride therapy, however, excellent results were obtained with both mercurin suppository and intravenous salyrgan. In both these latter instances larger doses of the mercurials were given. In this case there also was a slight rise in the CO_2 combining power in the face of continued use of ammonium chloride, gr 90 daily. This observation was constant in the three cases in which these determinations were made.

Ethridge et al.⁸ found in studying the effect of inorganic salts on the diuretic action of salyrgan that the acidifying salts caused an increase in diuresis. They observed a moderate decrease in the CO_2 combining power

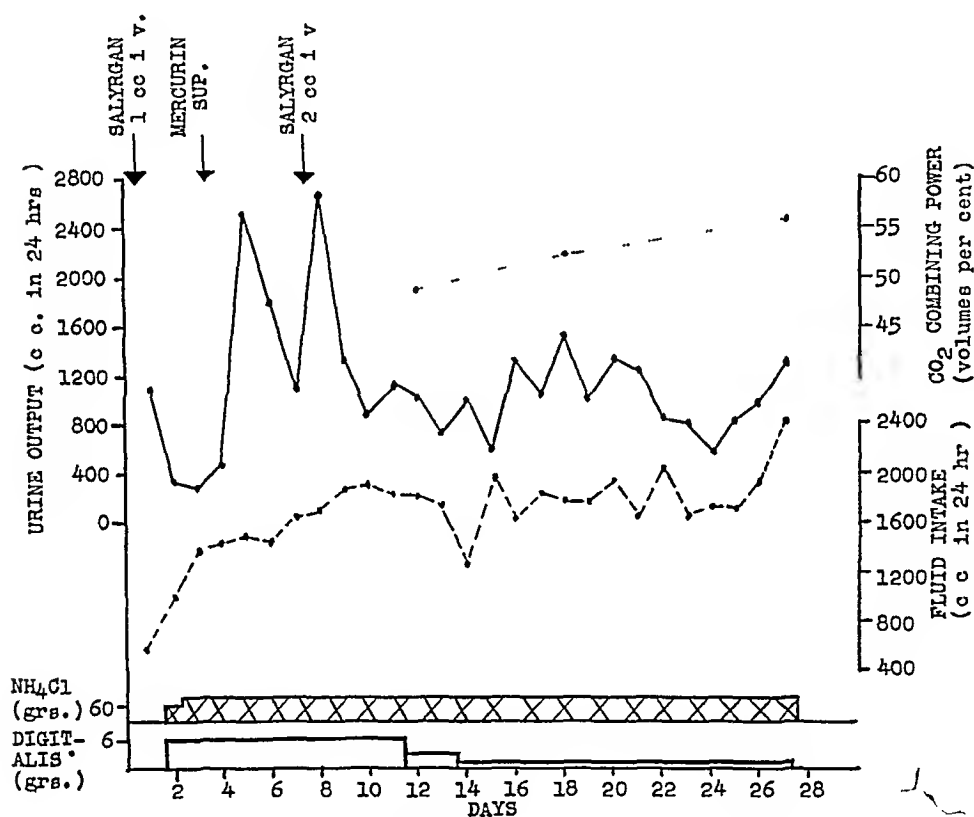


FIG 2 Case 5 Aged 51, M Arteriosclerotic heart disease

of the plasma of dogs three hours after the administration of ammonium chloride by stomach tube. They attributed the enhancement of the diuresis to this moderate acidosis.

Dennig et al.⁹ observed that patients who took large amounts of ammonium chloride daily developed a greater degree of acidosis on the second and third days of administration than subsequently even though the ingestion of the salt was continued.

Keith¹⁰ feels that the change in the CO_2 combining power is not of sufficient magnitude to account for the increase in diuresis when the acid

forming salts are given. He believes that the specific action of the acid radical is an important factor.

The findings reported in this protocol tend to minimize the importance of reduction of the CO_2 combining power.

Case 6 (Figure 3) A II, male, aged 62, had first noted shortness of breath six months prior to admission. Because of this complaint he had been forced to

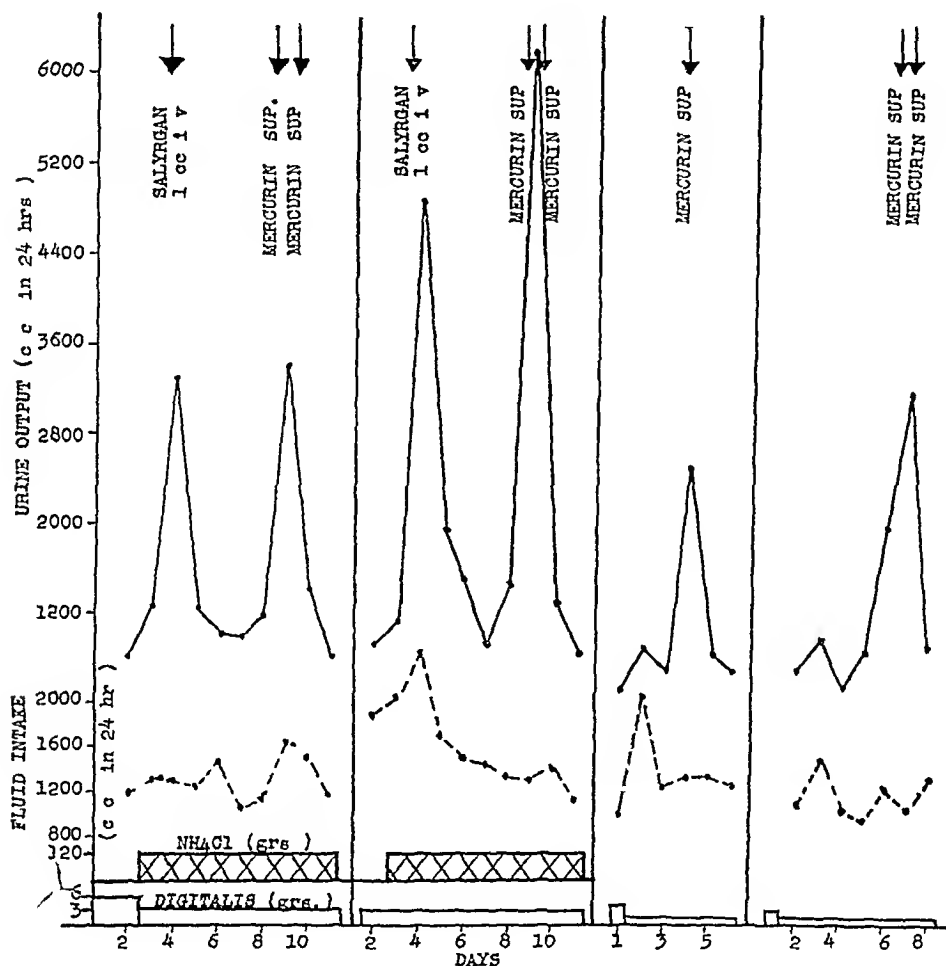


FIG 3 *Case 6* Aged 62, M Syphilitic and arteriosclerotic heart disease
Case 7 Aged 30, M Hypertensive cardiovascular disease
Case 8 Aged 67, M Arteriosclerotic heart disease
Case 9 Aged 61, M Arteriosclerotic heart disease

limit his activity but despite this care his dyspnea became more severe. He had noticed edema of the ankles for two months. He had consulted his physician at the start of his complaints and the doctor had told him that his blood pressure was "195". The patient stated that at times he had spots before his eyes and roaring in his ears.

The patient was not acutely distressed. Upon examination a bony growth was found on the hard palate. His teeth were carious and the gums were infected. His

tonsils were enlarged. Râles were heard over the bases of both lungs. The heart was enlarged to the left and the apex rate was 110. The blood pressure was 190 systolic and 120 diastolic. The abdomen was obese and edema of the ankles was present, graded two plus. The blood Wassermann test was four plus on two occasions. Fluoroscopy revealed a diffuse dilatation of the aorta.

Case 7 (Figure 3) P. M., male, aged 30, first noticed shortness of breath one year prior to admission. He had been put to bed for 14 weeks. Digitalis was administered, but was discontinued when he was allowed to leave his bed. For the three weeks preceding admission he had suffered epigastric fullness, belching and constipation. He had a mild cough which caused pain in the right upper quadrant.

When observed the patient was sweating profusely although not in acute distress. He was moderately obese. Râles were present in both bases posteriorly. The heart was moderately enlarged to the left, the pulse was 115, gallop rhythm and an occasional extrasystole were noted. The blood pressure was 165 systolic and 135 diastolic. The abdomen was moderately obese and the edge of the liver was definitely palpable and quite tender. The lower margin of the spleen was felt at the costal margin. Edema of the lower extremities and over the sacrum was of moderate grade.

In case 5 (figure 2) and cases 6 and 7 (figure 3) a comparison between the efficacy of mercurin suppositories and intravenous mercurials may be drawn. An approximately equal degree of diuresis was obtained with each method, but a greater amount of mercury was administered in the suppositories.

Case 8 (Figure 3) H. M., male, aged 67, was brought into the hospital acutely ill with orthopnea and cough. He had had "bronchitis" for years, but, several weeks before, he complained of a moderately severe, non-radiating pain over the heart which had persisted for several days. Following the pain the bronchial symptoms became worse. On the night of admission the patient had a severe seizure of coughing with production of pink, foamy sputum and marked shortness of breath. His face became cyanotic and he appeared in great distress. The chest was emphysematous with a precordial bulge. Wet, rattling râles were present throughout both lungs. The heart was enlarged to the right and left, the rate was 120 and the rhythm totally irregular. The blood pressure was 130 systolic and 70 diastolic. The liver edge was palpated 4 cm. below the costal margin and was not tender. There was no edema. The patient responded promptly to venesection and stimulants. An electrocardiogram showed auricular fibrillation, and premature ventricular contractions, evidences of coronary occlusion were present. Fluoroscopic examination revealed a greatly enlarged heart and a diffuse, almost aneurysmal dilatation of the aorta. The blood Wassermann was repeatedly negative.

Case 9 (Figure 3) I. M., male, aged 61, complained of difficulty in breathing. He was a known mild diabetic and had had hay fever and "asthma" for 15 years. For the past year he had experienced gradually increasing weakness, dyspnea, and swelling of his ankles. Also he had complained of belching for the past three months. The patient was obviously dyspneic and coughed frequently. Fine râles were heard over the right side of the chest but no asthmatic wheeze was apparent. The heart was enlarged to the left and the tones were distant and muffled. An occasional extrasystole was present. The pulse was regular, rate 100, blood pressure 114 systolic and 70 diastolic. The abdomen was negative except for the liver which was easily palpated. Pitting edema was found upon examining the extremities. The diabetic state was found to be under control. The chest signs and respiratory symptoms disappeared in response to cardiac therapy.

Case 10 (Table 1) E. M., male, aged 44, stated that he had had an attack of rheumatic heart disease at the age of 35. At that time he had shown all the symptoms and signs of cardiac decompensation and had been told that he had murmurs. Later he was informed that his recovery was complete. A few weeks prior to his admission he had a mild cold which was followed by pounding of the heart, shortness of breath, and swelling of the extremities. The patient showed marked pallor, dyspnea and orthopnea. Rales were present throughout both lungs. The heart was enlarged to the left. Pulse rate was 140, rhythm totally irregular. The blood pressure was 135 systolic and 65 diastolic. The liver was palpable and tender. Extremities were edematous. No petechiae were found. The temperature was 101° F by rectum. An electrocardiogram proved the cardiac irregularity to be auricular fibrillation.

The urinalysis of this patient on admission yielded findings typical of chronic passive congestion. Specific gravity 1.020, albumin plus, 3-5 red blood cells per high power field (centrifuged). A mercurin suppository was given on the second day but the patient showed only a slight, if any, increase in urinary output and this questionable increase was delayed until 48 hours after the administration of ammonium chloride had been begun. A second mercurial suppository was given on the ninth day, and 48 hours after its administration (and six days of ammonium chloride therapy) the patient suddenly became disoriented, had thick speech and hyperpnea. He complained of double vision, and there was paralysis of the fourth cranial nerve. He was thought to have had a cerebral embolus. The urine the next day contained innumerable red blood cells, gross hematuria continued for a month and microscopic hematuria persisted until the patient's death. The patient had a rising blood pressure from 135 systolic and 65 diastolic to 184 systolic and 85 diastolic, a rising azotemia up to a level of urea nitrogen of 49 mg per cent, and of non-protein nitrogen of 75 mg per cent. The urea nitrogen to non-protein nitrogen ratio was 0.65. The blood cholesterol dropped from 185 mg per cent to 155 mg per cent, the CO combining power at the time of the acute episode was 29.6 volumes per cent. The specific gravity of the urine on 22 separate specimens ranged between 1.010 and 1.016. The anemia increased. The blood chemical data and the urinary findings at this time pointed to rapidly contracting kidneys such as are found in a fulminating type of diffuse glomerulo-nephritis. An intravenous urogram two weeks prior to death was unsuccessful because of inadequate concentration of the dye in the kidneys. The auricular fibrillation persisted as did the diplopia and the thick speech. The patient died 10 weeks following the first cerebral embolus. He complained of headache, lapsed into coma with stertorous breathing, hyperreflexia, increase in edema and multiple petechiae on the lower extremities. (These were the only petechiae ever observed during the patient's entire illness.) The patient died 24 hours later. Permission for autopsy was denied but the cause of death was thought to be a second cerebral embolus.

Keith¹⁰ pointed out that hematuria and renal insufficiency has occurred, though rarely, from the injection of organic mercurials. He also observed that ammonium chloride may induce a mild renal insufficiency which is usually temporary in duration.

Case 11 (Table 1) T. C., male, aged 33, had been a known luetic for 12 years. Six weeks prior to admission the patient had received the last of 12 doses of arsphenamine. For the 10 days preceding admission the patient complained of an increasing yellow tinge to his skin and of vague abdominal pain.

Physical examination was negative except for marked icterus and slight tenderness in the right upper quadrant. Chemical studies supported the history by indicating the presence of a toxic hepatitis. In the second week in the hospital the

patient complained of a distended abdomen and by the eighteenth day free fluid was detected. During the third week the patient called attention to discomfort in his rectum. Following the onset of the ascites, he had developed large, tender hemorrhoids.

Case 12 (Table 1) G. G., male, aged 58, had had pain in the upper abdomen for two months. The pain was not severe but annoying, and his "asthma" which he had had for several years became increasingly worse. He also had been aware of increase in his abdominal girth and his legs were markedly swollen. The patient's face was covered with spider telangiectases and it also had a slight icteric tinge. Rales were present throughout the chest. The heart was enlarged to the left and a systolic murmur was heard over the entire precordium. The pulse rate was 92 and regular, the blood pressure was 155 systolic and 85 diastolic. There was an umbilical hernia present and the abdomen was distended with fluid. The liver was firm, non-tender, and palpable on ballottement. The lower extremities were markedly edematous. The patient had large, tender, protruding hemorrhoids. During the course of treatment the rales and edema disappeared in response to cardiac therapy but the ascites increased. Frequent paracenteses were of only transient aid. The patient developed a psychosis during his illness with paranoid manifestations. Chemical studies revealed an icteric index ranging from 14 to 30, normal figures were found for urea nitrogen, amino acids, non-protein nitrogen and cholesterol. The cause of the persistent ascites was considered to be hepatic cirrhosis. The patient's course was downhill in spite of all therapy. Permission for autopsy was denied.

In cases 11 and 12 (patients with hepatic cirrhosis, ascites and hemorrhoids), the suppositories caused discomfort because of the rectal lesions. In case 11 the suppositories were expelled within 20 minutes because of the local distress. In this case, however, there was a diuresis but it may have resulted from the ammonium chloride which the patient also was receiving. In case 12 mercurin suppositories on four occasions failed to result in diuresis. Intravenous injection of 2 c.c. of mercupurin caused no increase in urinary output in one instance but on a subsequent injection an output of 2,050 c.c. was obtained. This patient was quite refractory and refused ammonium chloride in solution or as enteric coated pills. The ascites in cirrhosis cases does not respond well to mercurials intravenously and with impaired absorption and brief time of retention of the suppositories it is not surprising that the rectal route of mercury administration was not efficacious in these two cases.

SUMMARY

Mercurin suppositories were used on 20 occasions in 10 patients with varying degrees of cardiac decompensation. These patients were routinely treated by bed rest, sedation, digitalis and restricted fluid intake. In 17 instances (85 per cent) a diuresis ranging from 1,950 c.c. to 8,750 c.c. in 24 hours resulted from the use of the suppositories. In one of the failures (case 2, table 1) the diuresis was delayed following the suppository administration until the third day of ammonium chloride therapy. The other two failures were obtained in case 10 (table 1) which showed renal complications. Renal insufficiency followed the mercurial suppositories and

ammonium chloride administration in this case but the subsequent death apparently was caused by a cerebral embolus

In the two cases of hepatic cirrhosis studied, mercurin suppository did not seem to be the best form of mercury administration because of the rectal discomfort and the lack of consistent increase in urinary output

CONCLUSIONS

1 The mercurin suppository is an effective diuretic agent in selected cases

2 It is most efficacious when used in conjunction with ammonium chloride. Ammonium chloride is a valuable adjunct and in some cases essential to the production of a satisfactory diuresis. In three cases in which the CO_2 combining power was observed at intervals, ammonium chloride had a marked synergistic diuretic effect even though normal or elevated CO_2 combining powers were present

3 Mercury is a renal irritant and its use in any form should be carefully controlled by frequent urinalyses

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SOME PUBLIC HEALTH ASPECTS OF UNDULANT FEVER *

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IN this brief discussion undulant fever is treated as a public health problem in order to bring out a few points concerning the diseases in lower animals from which the human being derives his infection. It is felt that to many medical men more information concerning the manifestations of this disease in domestic animals will be of interest.

Considerable confusion exists over the terminology. Malta fever, undulant fever, brucellosis, brucelliasis, Mediterranean fever, Bang's disease and many other terms are employed. Similarly there has existed among bacteriologists considerable controversy over the classification and relationship of the bacteria present in the lower animals afflicted with this disease or group of diseases.

For practical purposes there seems to be enough agreement to permit calling this entire group of fevers the brucella group, reserving the term undulant fever for the clinical disease seen in man, which is apparently the same disease regardless of the source of infection. Similarly, there is considerable agreement as to the classification of the three main species of bacteria etiologically responsible. These are *Brucella melitensis* causing Malta fever in goats, *Brucella abortus* causing contagious abortion in cattle, and *Brucella suis* producing abortion disease in swine. As previously stated, infection with any of these three results in undulant fever in man and the disease appears to be the same regardless of its source.

Experimentally brucella infection can be produced in any warm blooded animal, but the three diseases mentioned above are the only ones with which we need be seriously concerned.

In America the milch goat can be dismissed as being a very minor factor in the spread of undulant fever, although a few cases have been traced to imported goats, and several years ago a serious outbreak occurred in the southwest where European goats had been introduced on a fairly large scale commercially.

Granting that this source is a minor one, the history of Malta fever is too interesting and has added too much to our knowledge of brucellosis in general to be disregarded completely. (Incidentally, the term Malta fever was objected to so strenuously by the Maltese that the League of Nations Health Organization changed the name to undulant fever in their official list of diseases.)

The fever has been known for centuries in Mediterranean countries. In fact Hippocrates described a fever which historians now recognize as being Malta fever. During the eighteenth and nineteenth centuries various accounts of the disease appeared and during the Crimean war considerable confusion existed due to the simul-

* Received for publication May 25 1937

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taneous presence of Malta and typhoid fevers in the British troops. The disease was first found to have a specific etiology in 1886 when Colonel Bruce¹ described a small cocco-bacillus seen in sections of spleen and the following year isolated the bacillus from human cases found on the island of Malta. He seems to have been the first to name the organism *Micrococcus melitensis*.

The next big step in studying the disease took place in 1897 when Wright and Semple² showed that it could be diagnosed by agglutination with the blood serum of infected animals.

In 1904 a commission was appointed by the British admiralty, the war office and the civil government of Malta to study the problem. Among their most important findings may be listed the fact that over 40 per cent of the goats on the Island of Malta were infected and that a big percentage of these were eliminating virulent bacteria in their milk. Human cases were traced to drinking such milk. Many other cases were found in herdsmen and those handling the infected animals. Many of these were found to have been infected through skin abrasions contaminated with urine from infected goats, in which large numbers of organisms were found.

In the commission's final report they stated that the most common method of infection in man was by the ingestion of infective articles of food, mainly milk.

When we come to consider contagious abortion in cattle and swine we find a more serious source of danger to man. This disease in animals has been reported from every civilized country and in America it has long since surpassed tuberculosis of cattle as an economic problem. It is this point of great prevalence which I wish to emphasize for I am sure it is not generally appreciated by the medical profession. We are accustomed to regard undulant fever in man as a comparatively rare condition and thus may lose sight of the fact that the possibilities for infection are almost unlimited.

The various states cooperating with the Bureau of Animal Industry are at present engaged in a vast control program which includes blood testing of large groups of dairy cattle. Without quoting any mass of data, I should like to give the figures for Missouri for the two year period ending October 31, 1936. Approximately 52,000 herds were tested in this state and infection was found in over 16,000 of them. Out of 640,000 cattle tested, 52,000 were found to be infected. These figures indicate in general what was found for the entire country in which over twelve million cattle were tested during this period and approximately one million reactors were found.

In a short discussion it is impossible to give more than a sketchy outline of the disease in cattle. Briefly the outstanding feature, as the name implies, is actual abortion in the gravid animal. The abortion is brought about by active inflammation within the uterus and the fetal membranes. A given animal may abort one or more times and then usually develops enough immunity to carry subsequent pregnancies to term.

Unless the uterus becomes invaded with other organisms which produce metritis and future sterility, actual illness is not apparent. The severe constitutional upsets seen in the human do not occur in either cattle, swine or goats. The bacilli live a more or less innocent existence within the body of the animal and are spread to the outside world in the lochial discharges.

of the aborting animal, in the urine and feces, and through the milk where they appear continuously or in frequent showers. A microscopic mastitis without signs or symptoms is usually found in these animals. Rarely the male is found to react, the infection being present in the glandular systems, chiefly the testes. In cattle the disease spreads from animal to animal chiefly from contaminated pasturage or by means of infected food, the infection being spread chiefly by way of the gastrointestinal tract. The bacilli will remain alive and virulent for as long as four months in damp soil shielded from direct sunlight.

The disease in swine shows much the same clinical picture and needs no special mention.

Dr Alice Evans³ of the Dairy Division of the Bureau of Animal Industry was the first to point out the similarity between the *Micrococcus melitensis* of Bruce and the bacillus of contagious abortion first isolated by Professor Bernard Bang⁴ of Copenhagen in 1897 and now usually called the Bang bacillus. She showed that the two are so similar as to be indistinguishable by ordinary laboratory means. Regardless of the source of infection, undulant fever runs the same course in man and routine agglutination methods will not suffice to determine which species is present. How recent is the knowledge that abortion disease in cattle could result in undulant fever in man is shown by a statement made by Dr Evans in her 1918 article. In her discussion she states that "Since infection is dependent on the amount of infectious material, it may be that this difference in the number of bacteria in the milk of the two species of animals may account for our freedom from disease when cow's milk containing *Bacterium abortus* is consumed. On the other hand, are we sure that cases of glandular disease, or cases of abortion, or possibly diseases of the respiratory tract, may not sometimes occur among human subjects in this country as a result of drinking raw cow's milk?" This prophecy was made only 17 years ago and has proved only too true. We now know that brucella infection can and does attack every tissue and organ in the human mechanism. Ironically as it may seem, Dr Evans herself was soon to prove how accurate her own surmise was.

Since such abundant opportunity to become infected exists, we may well ask why more cases are not reported. One reason I am sure lies in the fact that many cases are never diagnosed. Many of the cases which are diagnosed have been treated for other things first. This is especially apt to occur in communities where laboratory facilities for making serological tests are not easily available. The tendency of the infection to produce tender and swollen joints makes it easy to confuse with arthritis. Many cases start with the step-ladder rise in temperature characteristic of typhoid. Chills with a daily rise in temperature are certainly suggestive of malaria and apt to be treated as such in the absence of proper blood examination. Another reason we do not see more of this disease is the fact that so much

milk consumed by the public is pasteurized. Proper pasteurization readily destroys the bacillus.

It is a well known fact, readily apparent clinically, that there is a great variation in the virulence of individual strains of the Bang bacillus found throughout the country. Occasionally a strain is encountered of such high virulence that practically every animal of breeding age in a herd will become infected and abort. At the other extreme is found a strain, isolated years ago by Huddelston, which he called an avirulent strain and which he used with impunity as a living vaccine in attempting to build up immunity in non-infected cows. This fact being true, whether an individual becomes infected probably depends to some extent upon how virulent a strain he encountered when the infected milk was consumed.

Infection with *Brucella suis* or the porcine strain is found chiefly in herdsmen, veterinarians, butchers and packing house workers who come into contact with infected animals or who handle the meat after such animals are slaughtered. In such cases infection probably enters through cuts and abrasions in the skin which have become soiled with the excreta of the living animal, or with the blood and tissue juices of the animals on their way through the various steps of packing house routine.

Undulant fever is diagnosed by the agglutination or complement fixation tests and by allergic skin reactions with culture filtrates such as the Brucellin of Huddelston. Cultural methods and guinea pig inoculation are valuable experimentally but too slow for routine clinical use. My own preference, based entirely upon tests in domestic animals, has always been for the complement fixation test in spite of its more involved technic. While it has now been practically discarded in favor of the much quicker and simpler agglutination test, I still have a feeling that it is the more accurate method. In man it is not uncommon to get a negative agglutination reaction on a patient known to be infected. In such a case the skin test will often be positive. On the other hand, positive agglutination does not always mean that the patient is actively infected. Some difference of opinion exists as to how low the dilution should be carried. Some laboratory technicians report any agglutination at all as being evidence of infection. In early work on Bang's disease in cattle, we disregarded agglutination in dilutions of $\frac{1}{320}$ or below as being false reactions. Ample clinical proof was available to support this stand.

It was formerly thought that agglutination in human serum might be due sometimes to ingestion of preformed antibodies present in milk since such antibodies are present in milk from practically all infected cows. This type of reaction has since been denied and the statement made that such antibodies cannot pass through the walls of the digestive tract. In this connection I should like to recall briefly an experiment I helped to conduct many years ago. We found routinely that just prior to calving most positively reacting cows lost their positive reaction and remained negative for

many weeks. The colostrum milk at this time, however, was found to be almost unbelievably rich in immune bodies. It appeared that the protein fraction of the blood serum which carried these immune bodies had become concentrated in the colostrum and stored there. When these cows calved, if such calves were bled and tested immediately, before nursing their mothers, their serum always gave a negative reaction. If kept permanently from their mothers such calves could be raised by hand on other milk and reached maturity without ever giving a positive reaction. If, however, they were allowed to nurse, blood serum drawn two or three hours later always gave a strongly positive reaction. Similarly, calves from negative mothers, if given colostrum rich in antibodies, would show the same thing. Of course, the digestive tract of a young calf is entirely different from that of a man but it is hard to see how these newborn animals could ingest virulent infection and immediately develop enough immune bodies of their own to give strong serological reactions two or three hours later. It seems more logical to believe that preformed antibodies did pass through the intestinal wall barrier. If virulent cultures were given by mouth or hypodermically 10 or 12 days had to elapse before immune bodies could be detected in the blood.

In the matter of treatment the veterinary profession has practically run the gamut of drug and biological products with but scant success. Dean Giltner, previously quoted as being an outstanding authority, stated in a recent publication that "Curative treatment of brucellosis by the use of drugs or chemical has signally failed." All manner of bacterines, vaccines and sera have been used with occasional encouraging results but nothing has been devised which can be generally counted on for definite results. This therapeutic failure has greatly stimulated control programs which have for their goal the ultimate elimination of the disease by destruction of less valuable animals and isolation of those reactors too valuable to sacrifice. Healthy progeny can be raised from infected stock if removed from sources of contagion prior to reaching breeding age. By means of wholesale blood testing and proper sanitation it is hoped to establish accredited abortion-free herds and eventually to rid the countries' dairy and beef herds of this malady. Cooperation on the part of stock breeders will eventually be gained through necessity. Even now it is becoming practically impossible for a breeder to sell a pure bred animal without a negative blood test. Certified milk can be placed on the market only if the animals supplying it can be shown to be free from tuberculosis and abortion disease. Rigid restrictions against interstate shipment of infected cattle are now in existence in most states. Such restrictions have gone a long way to correct abuses which formerly existed. That such programs must go forward against tremendous odds goes without saying, but marked progress is being made.

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PROTAMINE-ZINC-INSULIN IN DIABETES¹

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THE observations reported in this paper were made in the management of 60 patients, some of whom had been treated with various preparations of protamine-insulin since February 1936. Since August 1936, all patients in this group have received protamine-zinc-insulin. Cases of all degrees of severity have been treated and four children are included in the group. The ages of the patients vary from 8 to 76 years.

It has been felt advisable to hospitalize all patients during the first part of their treatment. The hospital stay averaged 18 days. No patient was confined to bed except for some complication. An attempt was made in each case to maintain physical activity comparable to that of the patient's average day. During the hospital stay, venous blood was taken routinely for determination of the blood sugar at 8 a.m., 12 noon, 4 p.m., and 10 p.m. daily and in some cases at other hours in addition, a modification of the Myers-Bailey method being used. Twenty-four hour specimens of urine were collected in four periods daily, the periods ending before meals and at bedtime. Each specimen was tested for sugar by Benedict's qualitative method and when sugar was present, the 24-hour excretion was calculated in grams, Benedict's quantitative method being used. Qualitative estimation of ketone bodies was done on all urine containing more than 1 per cent glucose.

THE INSULIN

The protamine-zinc-insulin used in this investigation contained 40 units of insulin per cubic centimeter and approximately 0.08 mg. of zinc in combination with protamine in a buffered solution. Since the active material is present in fine particles, careful, gentle mixing is important before the withdrawal of each dose. The use of a cool, dry syringe is advised and it is recommended that subcutaneous injection be done in such a way as to insure a depot of precipitated insulin in the subcutaneous tissues. The material was supplied in 5 c.c. vials, each vial bearing the date after which its stability could not be guaranteed.[†]

THE DIET

We have been accustomed to use a high carbohydrate, relatively low fat diet for some years and this practice has been continued. In our attempt to control diabetes of various degrees of severity with one dose of protamine-zinc-insulin, we have in some cases tended to be less rigid regarding the low

* Received for publication May 3, 1937.

[†] The protamine-zinc-insulin used has been generously supplied through the courtesy of Dr. F. B. Peck and the Eli Lilly Company.

level of fat which is usually maintained in such diets. The number of grams of fat per day in the routine diet was 60. It is our impression that a smooth control is more readily obtained when the carbohydrate content of the diet is not elevated above 200 grams per day. Some patients have received 250 grams of carbohydrate per day and the carbohydrate intake has been 175 grams per day or more in 42 of the patients. The average daily intake in the entire group has been carbohydrate, 182 grams, protein, 66 grams, and fat, 75 grams.

The diet for each individual is calculated on the basis of the basal caloric requirement for ideal weight. In obese individuals, we have not usually found it advisable to use a daily caloric intake below such a figure, as this is usually considerably less than the basal caloric requirement for actual weight and thus produces a daily caloric deficit sufficient to maintain loss in weight where this is required. In most instances, the total caloric intake ranges between the basal caloric requirement for ideal weight and 40 per cent above it.

The diet has been divided routinely into three meals containing 30 per cent, 35 per cent, and 35 per cent respectively of the available glucose for the day. Considerable manipulation of this distribution is advantageous at times. With the use of protamine-zinc-insulin, it has not been found to be of frequent advantage to use one meal containing only 20 per cent of the daily available glucose as was advocated by Hagedorn, et al.,² and Root, Marble, et al.,³ using plain protamine-insulin. In some cases we have divided the daily intake into four meals, giving a small proportion of the food as a luncheon at bedtime. This has the advantage of creating more even intake of food throughout the 24 hours and thus offsets to some degree the tendency to fasting hypoglycemia. In those cases in which there is an undue rise of blood sugar by noon, it is an advantage to deduct the food for the bedtime lunch from the regular breakfast.

DURATION OF ACTIVITY

Estimates of the duration of activity of a single dose of protamine-zinc-insulin in the human have been obtained from four types of observations.

1. The effect on the blood sugar level of a single dose given with one meal after which the patient is required to fast until such time as the blood sugar level tends to rise again after the action of the insulin is diminished. By such a procedure in mild cases, hypoglycemia can be maintained for a period extending to nearly 30 hours.

2. The number of hours during which blood sugar levels in a diabetic can be controlled by a single dose when the patient is receiving regular meals. This type of observation applies obviously to those cases in which the diabetes is of such a degree of severity that the blood sugars are almost but not completely controlled by diet alone.

3 The third type of clinical observation which indicates definitely that the insulin compound acts for more than a day is the commonly observed cumulative effect of daily doses over the first three days of its administration

Figure 1 shows the effect of a single dose of protamine-zinc-insulin given at 7 a m , at which time a breakfast of 45 grams of carbohydrate 14 grams of protein, and 22 grams of fat was given after which the patient had no more food for 30 hours The distinct fall in blood sugar levels is obvious in from three to six hours and subsequently the fall is gradual and consistent The maximum effect is obtained 12 hours after administration Hypoglycemia is maintained in this case to the twenty-seventh hour In several observations of this type, the maximum effect appears in from 15 to 18 hours Larger doses, however, may maintain hypoglycemia for a much longer time, as in Rabinowitch's ⁴ case in which a single dose of

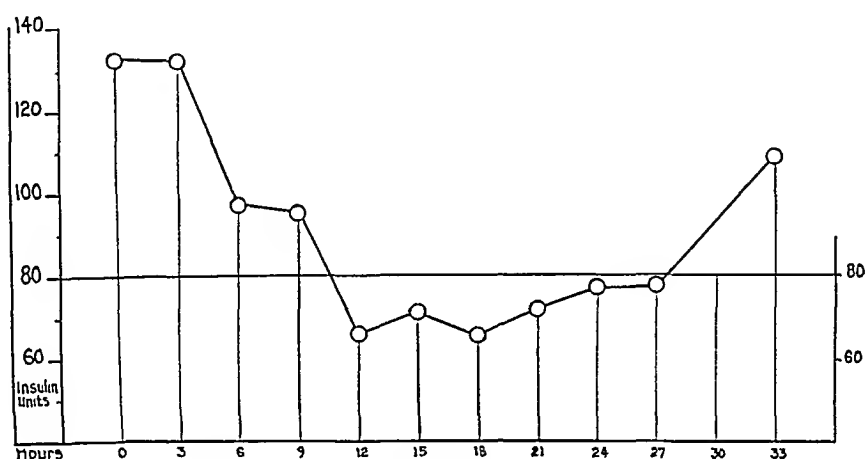


FIG 1

50 units of protamine-zinc-insulin maintained hypoglycemia for more than 36 hours

The second type of observation mentioned is visualized in figure 2 In this patient, the diet which contained C 100, P 50, and F 60, controlled blood sugar levels through the day except for the fasting levels which were 150 to 165 mg per hundred cubic centimeters A single dose of protamine-zinc-insulin was given on the morning of October 28 It will be noted on the chart that the fasting blood sugar levels were normal for two subsequent days, after which they rose to their original levels Another single dose of protamine-zinc-insulin at that time controlled the fasting blood sugar levels for two more days

The cumulative effect of daily doses of protamine-zinc-insulin is observed in nearly every instance in which the use of this material is begun The maximum cumulative effect usually appears to be most marked on the third day and is most obvious in comparing the fasting blood sugar levels

This appears to indicate that the dose given on the first of three days is still active to some degree on the third and also shows clearly why a reduction in dosage, as compared to regular requirements of insulin, usually is necessary

Figure 3 shows the blood sugar levels in a case in which fairly satisfactory control was obtained with three doses per day of regular insulin, the doses being given at 8 a m , 5 p m , and 10 p m . The first day depicted on the chart is a fairly typical representation of the previous control obtained, and it will be seen that the total required daily dose of regular insulin was 67 units . The patient had a mild afebrile infection of one great toe . She had been under control with regular insulin for two weeks prior to the use of protamine-zinc-insulin and had shown no significant alteration

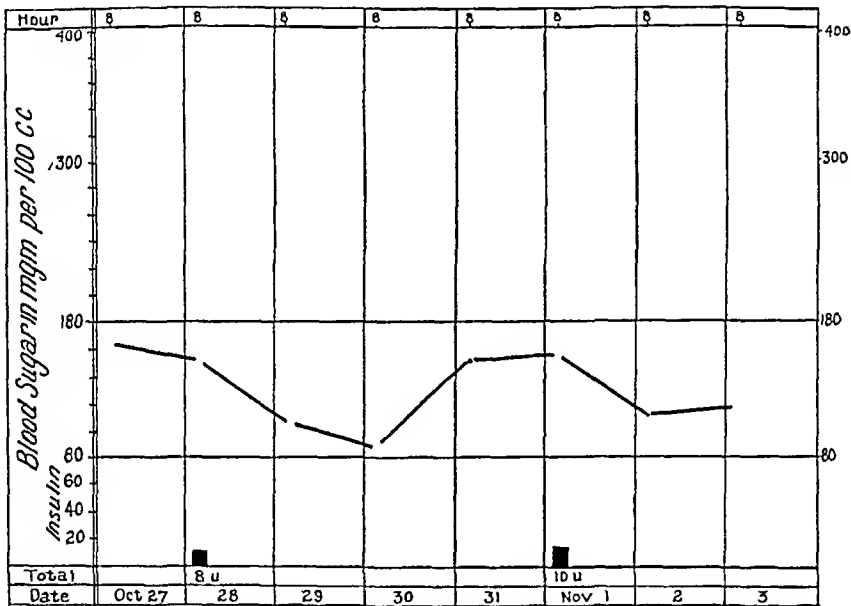


FIG 2

in necessary dosage . On the morning of November 3, 60 units of protamine-zinc-insulin were given in a single dose and this dose was repeated the following day . As will be seen, the fasting blood sugar level on the third day was distinctly lower than were those the first two days and on this day it was necessary to make an addition to the diet because of excessively low blood sugar levels . When the dose of protamine-zinc-insulin was reduced sufficiently to allow fasting levels to rise to the normal range, blood sugar levels during the day were not maintained at normal levels, indicating the necessity for an additional small dose of regular insulin . This patient was subsequently well controlled with a morning dose of protamine-zinc-insulin of 36 units, together with a dose of 6 units of regular insulin at noon

The cumulative effect of a single matutinal dose of protamine-zinc-insulin may be shown by examining the average fasting blood sugar levels in a series of patients during the first few days of control with this insulin as compared with the average fasting blood sugar level preceding its ad-

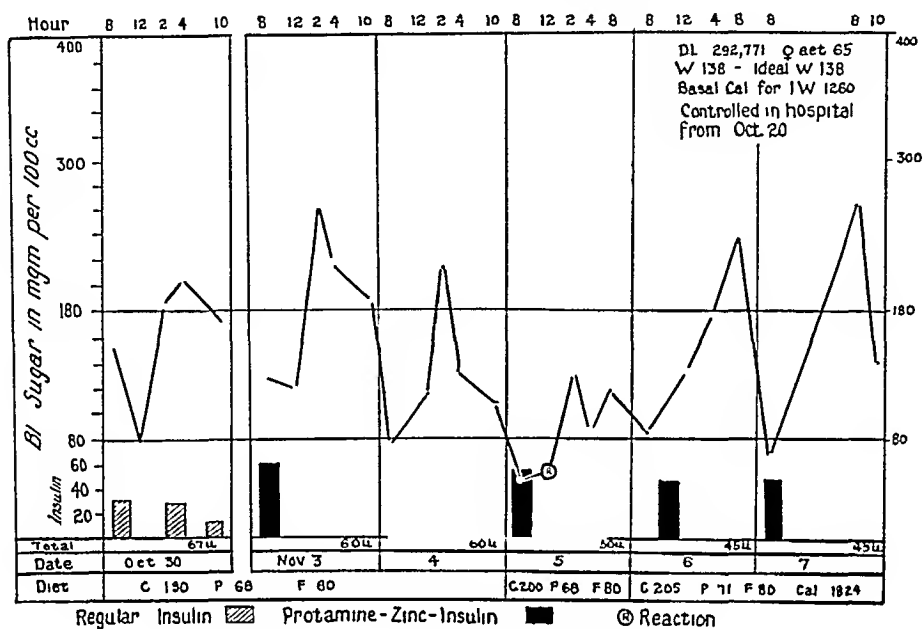


FIG 3

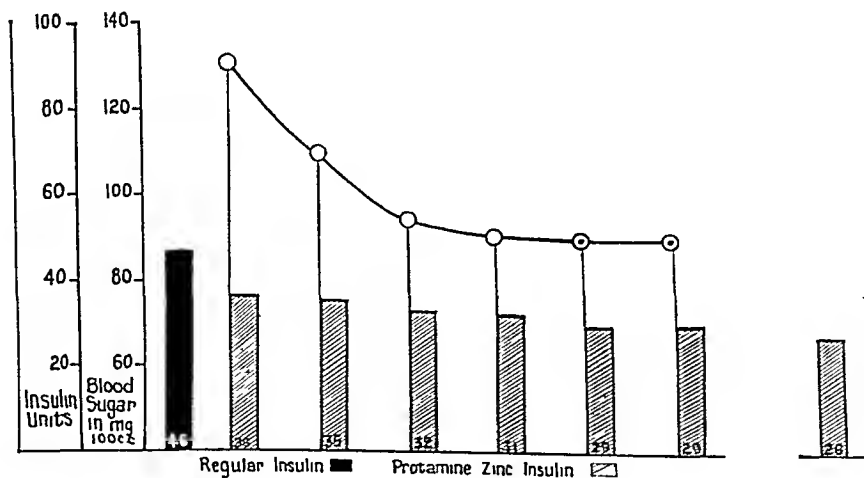


FIG 4

ministration (Figure 4) Fifteen cases were selected for this purpose. These patients were all under relatively recent control. The period of control with regular insulin in the hospital varied from 5 to 21 days and averaged 10.9 days before the first dose of protamine-zinc-insulin was given. During the period of regular insulin therapy, the diets were in-

creased in some of the cases but were at a fixed level for a period averaging 8.7 days. This dietary level was maintained throughout the period represented in the chart in all but one case in which it was raised because of insulin reactions. It was subsequently maintained at the new level.

The average reduction in total dosage of insulin is shown in the chart. In spite of the reduction in dosage, there was a distinct reduction in fasting blood sugar levels which was most obvious during the first three days. The detached block at the end of the chart indicates the amount of protamine-zinc-insulin necessary for control on the same diets at a period of from two to eight weeks later. As in other cases in the series, the reduction in dosage may fairly be ascribed in part to the fact that the patients had been under control for a short time only before the use of protamine-zinc-insulin. The fact that control was maintained in each instance on a dose suddenly reduced by about 20 per cent cannot, however, be explained on this basis and must be ascribed to the increased efficiency of the new insulin.

NUMBER OF INJECTIONS

Since the duration of activity of each dose of protamine-zinc-insulin is distinctly longer than 24 hours, there seems to be little or no advantage in giving more than one dose per day. A single dose per day usually is sufficient to control fasting blood sugar levels and the degree of depression of these levels apparently marks the limit of increase of the protamine-zinc-insulin dose.

TIME OF INJECTION

Although the duration of the effect of a single dose is longer than 24 hours, its effect is diminished in most instances after 18 hours. This being true, it seems advisable in most cases to give the single daily dose at a period longer than 18 hours prior to the low level of the day which usually is before breakfast regardless of the time of administration of the insulin. For this reason we have usually used the single daily dose before breakfast in each instance. In several cases in which the morning dose was shifted to before the evening meal, a further fall in fasting blood sugar levels was seen without any obvious advantage in control of the blood sugar levels during the day. In a few cases a second daily dose of protamine-zinc-insulin may be used to advantage and, in very severe cases, still better control may be obtained by supplementing one or both doses with regular insulin.

ESTIMATION OF THE DOSAGE

In estimating the dosage of protamine-zinc-insulin, two chief factors must be borne in mind: (1) that the effect is cumulative as shown above, and (2) for this reason the total daily requirement must invariably be less than the regular requirement of insulin. Due to improvement in control the required dosage may subsequently fall considerably. Where poor con-

tiol is present and rapid improvement can be anticipated, this cumulative effect may be dangerous if it is not considered carefully

Figure 5 shows the fasting blood sugar levels in a case in which control was poor while the patient was receiving 60 units of regular insulin per day. When the daily dose of regular insulin was raised to 80 units, the blood sugar levels fell somewhat but were still far above the normal range. Instead of first obtaining good control with regular insulin as we subsequently have found advisable, it was decided in this case to change to protamine-zinc-insulin, arranging a combination of protamine-zinc and regular insulin in such a way as to make the dose approximate 90 to 95 units per day. After the use of protamine-zinc-insulin for three days, the fasting blood

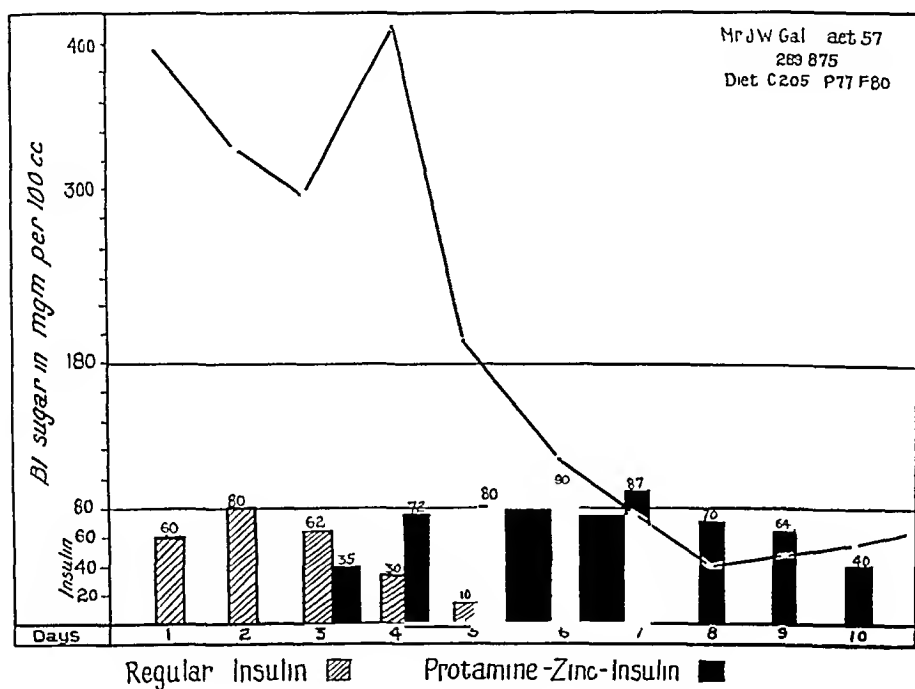


FIG 5

sugar levels had fallen to the normal range. The dosage was not reduced sufficiently at this time and the hypoglycemia which followed is apparent. It is interesting to note that no insulin reactions occurred. This case demonstrates the difficulty involved in estimating the proper dosage where good control is not obtained prior to the change from regular insulin to protamine-zinc-insulin.

When fairly stable control is first obtained with regular insulin, an immediate substitution with protamine-zinc can usually be made. However, we feel that the doses of protamine-zinc-insulin should seldom equal the doses of regular insulin and in cases of moderate severity it has been our practice recently to substitute a single dose of protamine-zinc-insulin of

about 80 per cent of the regular requirement of insulin. In the more severe case, considerable rise in blood sugar levels during the first few days is likely to occur. During this time, glycosuria is present but we have not seen acidosis of consequence during such a transition period. If the rise in blood sugar levels during the first two days of such a transition period tends to be excessive, it may be prevented by the addition of one or two doses of regular insulin which will not usually need to exceed more than 10 per cent of the previous requirement of regular insulin. Within a week, further reduction in insulin dosage is often necessary and in many of our cases even after leaving the hospital, further reduction may be found advisable within a period of two or three weeks.

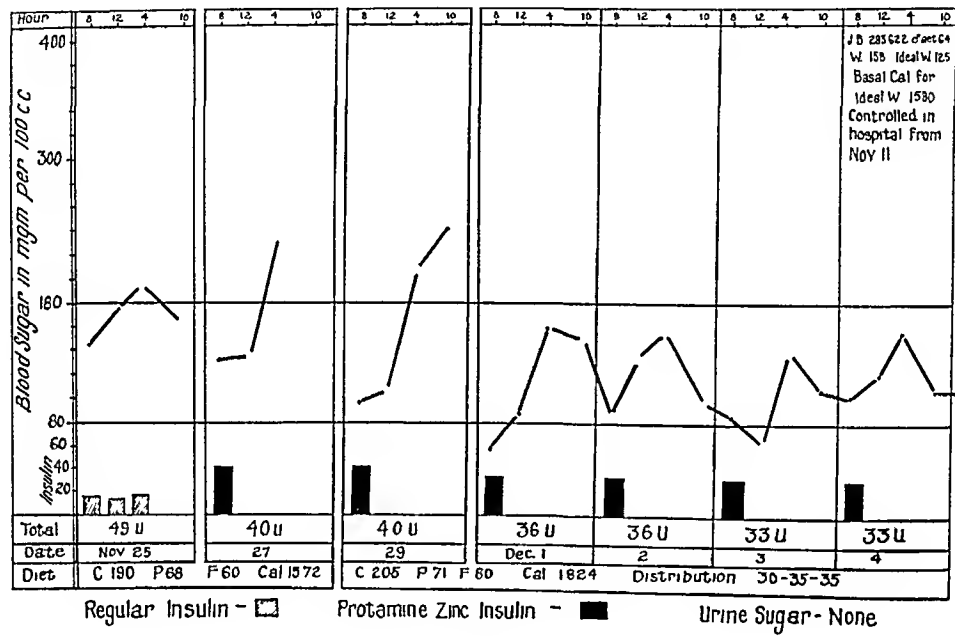


FIG 6

Figure 6 shows the blood sugar levels during a typical day of moderately good control with three doses of regular insulin, totaling 49 units. This patient was under control with regular insulin for 16 days prior to November 27. On November 27, 80 per cent of this dose, i.e., 40 units of protamine with regular insulin, was given as a single morning dose. The typical rise in blood sugar levels during the day for the first few days is apparent and the gradual fall in fasting blood sugar levels is also demonstrated. Subsequent reduction in dosage is shown and excellent control has followed the use of 33 units per day of protamine-zinc-insulin as compared to a less satisfactory control previously on 49 units per day of regular insulin.

Figures 7 and 8 show control for several days on diminishing doses of regular insulin, together with a smooth transition period and subsequent

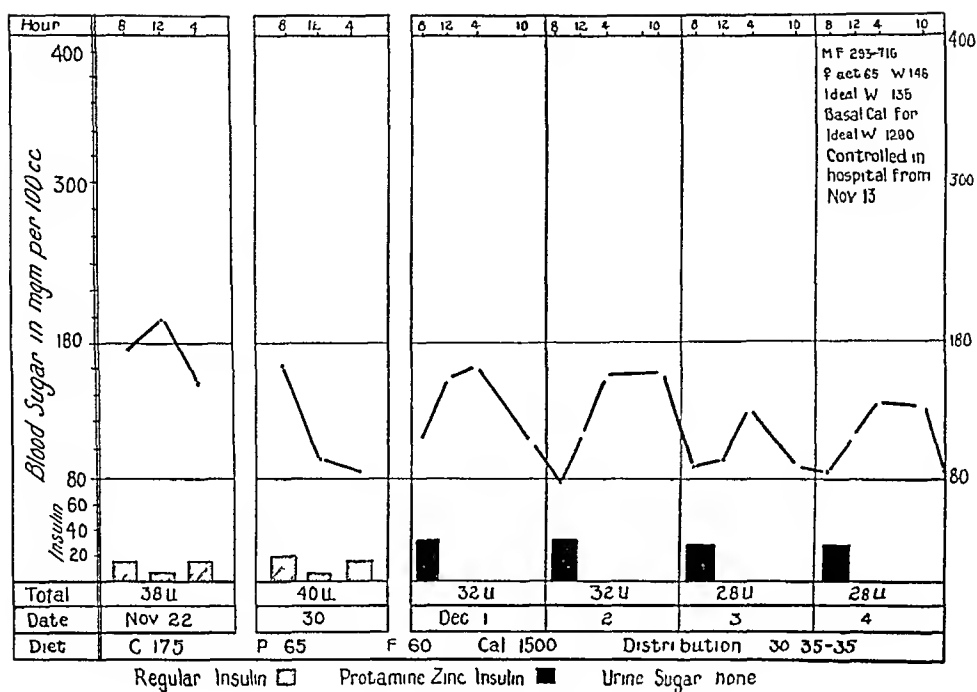


FIG 7

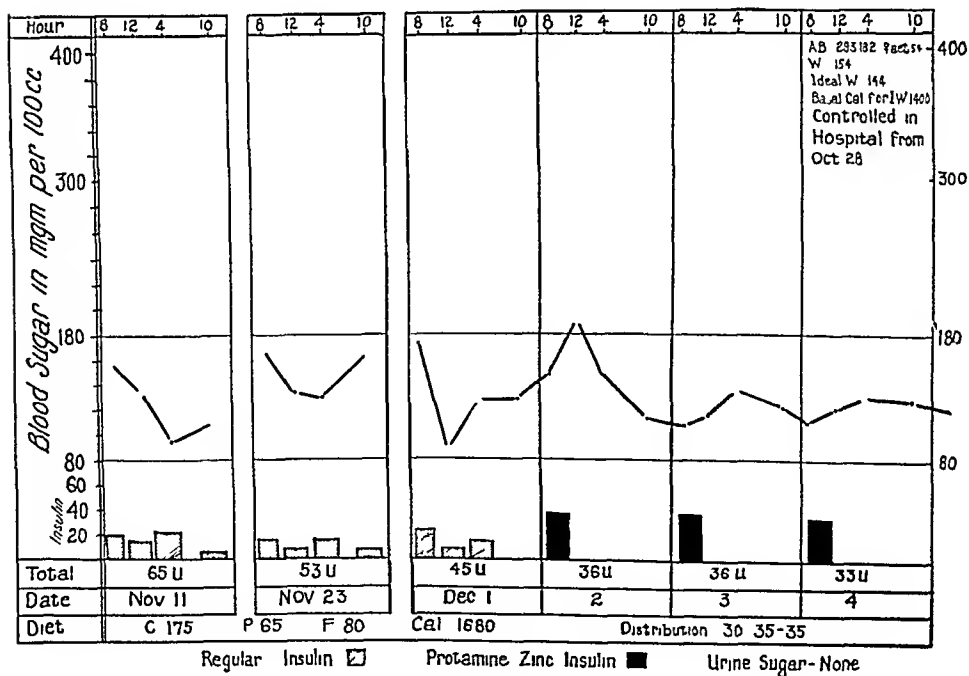


FIG 8

excellent control beginning with 80 per cent of the regular requirement of insulin with subsequent reduction in dosage

As indicated above, in mild cases where only the fasting blood sugar level remains high, this can readily be controlled by daily single doses of protamine-zinc-insulin and such control can be accomplished by doses as small as 5 units per day

Even in severe cases, the fasting blood sugar level will be the lowest of the day and, with sufficient dosage, it can be brought within normal range. If it is obvious, however, that the blood sugar levels during the day will not be controlled by such a dose, it will be necessary to add one or two doses of regular insulin. Such a case in which control was difficult is shown in figure 9

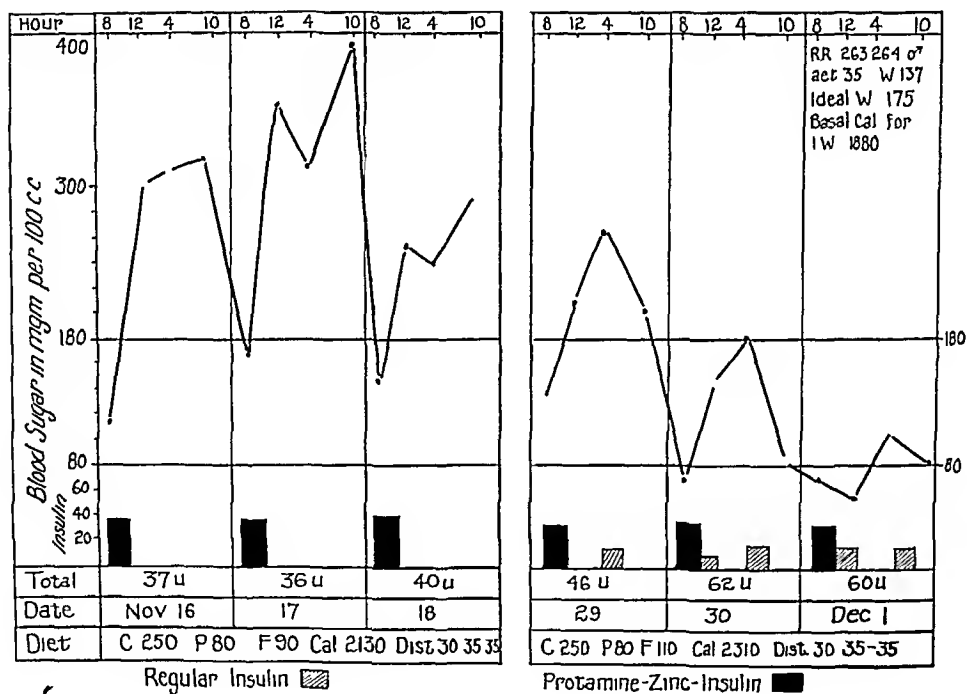


FIG 9

The general rules which we follow at present, therefore, in changing from regular to protamine-zinc-insulin may be summarized as follows

The patient is placed on a well regulated diet and good control is obtained with regular insulin. An immediate change is then made with a single morning dose of protamine-zinc-insulin which is approximately 80 per cent of the previous requirement of regular insulin.

If the blood sugar levels during the day are excessively high, about 10 per cent of the previous requirement of regular insulin is added. The dosage of protamine-zinc-insulin is then manipulated in such a way as to

obtain relatively normal fasting levels, changes in dosage not being made oftener than every third day. Subsequently, if morning reactions occur and if the fasting urine is sugar-free or if the fasting blood sugar levels are excessively low for two successive days, a reduction in protamine-zinc-insulin is necessary. If, on the other hand, sugar appears in the morning urine and if the fasting sugar levels remain high for more than two consecutive days, the protamine-zinc-insulin dosage may be increased. Where the fasting blood sugar levels are well regulated, one or two additional doses of regular insulin will be necessary if the blood sugar levels during the day persist at abnormal heights.

REACTIONS

It is a remarkable fact that with the use of protamine and protamine-zinc-insulin, the blood sugar level may reach 40 mg per hundred cubic centimeters or below without reactions. Reactions do occur, however, but for the most part they tend to be mild and gradual in their onset, thus allowing more time for treatment. Because of the gradual onset of such reactions, it is more difficult for the patient to detect an approaching reaction. Because of the prolonged effect of protamine-zinc-insulin, the reactions themselves are likely to be prolonged and to recur after treatment. Considerable hypoglycemia may occur without pronounced symptoms. It becomes more necessary than ever, therefore, to elicit any symptoms or signs which may be evidences of hypoglycemia. This is especially true in elderly individuals or in those with arteriosclerosis, especially arteriosclerotic heart disease. Fatigue, tingling, slight disturbance of memory, irritability, slight difficulty in speech, mild nausea, or headache should be suspected as possible symptoms of hypoglycemia. I have seen three severe reactions. One was associated with a convulsion, and this occurred in a child whose symptoms of hypoglycemia were present in this instance for nearly 12 hours. One occurred in a patient with severe diabetes which required 70 units of insulin per day. This patient lay down to rest after breakfast and was unconscious until he was awakened and found to be in obvious hypoglycemic shock at 5 a m the following morning. (He went to work as usual that day). The third patient took 50 units of insulin instead of 25 as ordered.

In the treatment of protamine-zinc-insulin reaction, it is advisable to use small doses of glucose or milk, to be prepared to repeat the treatment if necessary, and to avoid the use of excessively large amounts of sugar at one time.

REDUCTION IN DOSAGE AND IN NUMBER OF INJECTIONS

In 17 patients in this group, previous control had been good and had been maintained at a relatively stationary level for more than six months preceding the use of protamine-zinc-insulin. The average daily requirement of regular insulin had been 34.3 units while that of protamine-zinc-insulin was 22.0 units. In the older and better controlled cases, the reduction in

dosage is less than in the recently controlled cases. Of the entire group, the daily dose dropped from an average of 42.3 units of regular insulin to 25.4 units of protamine-zinc plus regular insulin.

Accessory regular insulin was necessary in 17 cases. The average number of daily injections necessary in the whole group was 2.8 of regular insulin as compared with 1.3 of protamine-zinc. This difference appears to be increasing with experience since, in the last 28 patients treated, the use of accessory regular insulin has been found necessary in only two instances. The average daily number of injections in this smaller group was 3.0 of regular insulin and 1.1 of protamine-zinc-insulin.

CONTRAINDICATIONS

The usually recognized contraindications are acidosis, infections, and pre- and postoperative care. Attempts are being made to determine the usefulness of protamine-zinc-insulin in these conditions but experience is not sufficient to warrant comments.

COMMENTS

Since the appearance of Hagedorn's paper in January 1936² his original claims that it had a prolonged action, gave better control in most cases, a tendency to less frequent insulin reactions with a diminishing number of injections and a reduction in actual dosage have largely been corroborated by other investigators^{3,4,5,6}. More recently, the addition of zinc to protamine-insulin has received considerable attention and it appears that the use of protamine-zinc-insulin has superseded that of plain protamine-insulin.

Although the advantages of protamine-zinc-insulin outweigh its disadvantages, the latter have not received sufficient emphasis. Better control can be secured with it in many cases but regulation, especially in the severe cases, is more difficult and will require a more intelligent grasp of the problem by the physician than has been necessary previously.

The comparative effectiveness of protamine-zinc-insulin should not be judged by blood sugar levels alone since, in some instances, it can be shown that even though the blood sugar levels fasting and four hours after meals are in good control, there may be more glycosuria than when the same levels are maintained with regular insulin. This appears to be due to the absence of the timely effect of insulin seen where regular insulin acts approximately synchronously with food absorption, as compared to the absence of this effect with protamine-zinc-insulin. It is remarkable that such increased glycosuria occurs infrequently.

Hospitalization for control is more important when protamine-zinc-insulin is used and usually will be more prolonged. Although reactions are less frequent, if they do occur, they are likely to be more difficult to detect and more prolonged.

In some of my cases reactions have occurred because the patient, having

taken a relatively large dose of protamine-zinc-insulin in the morning, has been unable to take all the food prescribed or has vomited part of the noon or evening meal. With regular insulin one would have the opportunity of reducing the noon or evening dose but this cannot be done with protamine-zinc-insulin. What effect this will have on the patient with arteriosclerosis remains to be seen. Some of the early disadvantages, such as instability of the solutions and the necessity of mixing them, have already been overcome.

Against these disadvantages we have more stable control, fewer injections, and lower dosage with protamine-zinc-insulin. It is hoped that, as a result of the better control, there will be a diminution in the incidence of hyperlipemia, liver disease, and degenerative disorders, especially arteriosclerosis. In these respects, the responsibility of the profession has increased.

SUMMARY

Protamine-zinc-insulin in common dosage appears to be active for 50 to 65 hours after injection. Its maximum effect is usually maintained between 12 and 18 hours. The prolonged effect of single daily doses makes it unnecessary usually to use more than one dose daily. The cumulative action increases to the third day or longer and reduces the requirement of insulin to less than 75 per cent of the dose of regular insulin in most cases. The number of injections, dosage, and the frequency of reactions are all reduced by its use. The most obvious advantage is in reduction in number of doses necessary. In all except two cases in which we have used it thus far, control has been as good or better than with regular insulin. It should be pointed out, however, that this improved control represents in some cases the combined use of protamine-zinc-insulin and of regular insulin. A normal fasting blood sugar level marks the limit of increase in protamine-zinc-insulin dosage. If, when this limit is reached, the blood sugar levels during the day remain high, one or more accessory doses of regular insulin are required for control. In some mild cases, a dose of protamine-zinc-insulin every second or third day may be sufficient to control fasting sugar levels.

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THE ASSOCIATION OF SCIATIC NEURITIS WITH LIVER DISEASE *

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PERIPHERAL neuritis occurs commonly in metabolic disorders such as gout and diabetes. In severe anemia, renal and hepatic diseases, on the other hand, the central nervous system is more frequently involved. Lenticular degeneration has been described in association with cirrhosis of the liver¹. Involvement of the peripheral nerves may also complicate liver disease. Polyneuritis has been ascribed to jaundice independently of a basic vitamin deficiency or alcohol abuse,² and also it has been thought due to the severe liver damage of biliary obstruction³. Neuritis has been noted in subjects with pigment cirrhosis, particularly in those with involvement of both the pancreas and liver⁴. Endogenous toxic substances resulting from hepatic insufficiency have been held responsible for causation of the neuritis.

This report of five cases indicates that the symptoms of sciatic neuritis in some instances may be a precursor of hepatic insufficiency. Though an analgesic effect of hepatitis and jaundice upon sciatic pain has been noted, the possible relationship between the jaundice and the antecedent sciatic pain has escaped notice. Such a relationship may be important, for the development of jaundice, sometimes fatal, has recently been ascribed to the use of cinchophen prescribed for its analgesic effect.

The following clinical observations suggest that sciatic neuritis may be an early manifestation of a disease process which may lead to liver disease and hepatic insufficiency. It is suggested that endogenous or exogenous toxic agents may affect peripheral nerves before their hepatic effects become manifest clinically.

CASE REPORTS

Case 1 B M, 48 years old, complained of bloating, belching and intolerance to fatty and fried foods of many years duration. For 18 months he had suffered a sensation of epigastric discomfort after meals. For six months he had suffered progressively more severe, cramp-like pains shooting down the posterior aspect of his left buttock, thigh, and calf. At times, only a feeling of numbness or discomfort existed. A month before admission to the hospital, the patient developed jaundice, darkly colored urine and clay-colored stools. He complained of generalized itching. His appetite failed him. He lost 10 pounds in weight. The only medication ingested by the patient throughout the course of his illness before admission to the hospital was ten grains of aspirin. With the onset of jaundice the pain in the left lower extremity became milder but did not disappear.

An enlarged, smooth, firm liver and an enlarged spleen were found on examination of the abdomen. Neurological examination revealed negative Patrick

* Received for publication May 20, 1937

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and Lasegue signs in the extremity affected with pain. The ankle jerk was present. The blood Wassermann reaction was negative.

Ascites and dependent edema developed. The patient lapsed into stupor and died despite intensive intravenous glucose therapy.

Necropsy confirmed the clinical diagnosis of subacute liver atrophy. The gall-bladder was normal in appearance and contained no stones. There was little evidence of hepatic regeneration microscopically. The pathological picture was also interpreted as a form of toxic cirrhosis. Unfortunately material was not obtained from the sciatic nerve in this case, or in case 4, for histological examination.

Case 2 S. M., aged 52 years, had received anti-luetic therapy. The last course of salvarsan had been administered five years before the hospital admission for diagnosis as to the cause of jaundice. For three weeks before the development of jaundice, the patient had suffered from severe pain in the posterior aspect of the right knee and thigh. Cinchophen had not been ingested.

The liver was enlarged and the spleen was not palpable. On neurological examination all reflexes were normal. The Kahn test was 3 plus.

The jaundice disappeared promptly. The sciatic pain subsided with the onset of the jaundice. The patient was ambulatory during his illness. In the four years since this illness, the patient has suffered no recurrence of sciatica.

The jaundice was classified as a so-called "catarrhal jaundice." In view of the fact that five years had elapsed since the administration of salvarsan, arsenic from this source was not considered in the etiology of the jaundice or sciatic neuritis.

Case 3 W. M., a physician, aged 45 years, had taken novatophan 18 years previously for severe sciatica. He had recovered from an attack of paratyphoid fever the year before. Splenic enlargement had been first noted 17 years ago, and liver enlargement had been known to exist for 14 years. For two years, left-sided sciatica had been present intermittently. Cinchophen had not been taken in recent years. For two weeks he had noted nausea and fever, and following this jaundice became evident. The sciatic pain subsided.

The liver and spleen were enlarged, and the laboratory tests indicated severe liver damage.

The patient ran a fever at the outset. Generalized itching was pronounced at times. After a protracted course, the jaundice subsided. The sciatic pain recurred after the acute phases of the illness had passed. It was believed that the patient has recovered from an attack of acute hepatitis superimposed upon an old toxic cirrhosis.

Case 4 R. B., aged 57 years, was admitted with a history of pain down the left thigh and leg of sudden onset and of eight weeks duration. After four weeks of pain of increasing severity, the patient had sought medical relief. She had been given six subcutaneous injections of Aolan, a milk preparation, and one intravenous injection of sodium iodide, without relief from pain. A single injection of 5 grains of cinchophen was then administered by a physician. One week later she developed icterus, anorexia, and epigastric distress. The stools became light in color. The sciatic pain definitely subsided with the onset of jaundice.

The liver was found enlarged, the spleen was not palpable. The Patrick and Lasegue signs were positive in the left lower extremity. The knee and ankle jerks were livelier on the right side than on the left.

The liver diminished in size as the illness progressed. Ascites and generalized edema developed and came set in despite intensive intravenous glucose therapy.

The necropsy demonstrated the presence of subacute liver atrophy and subacute pancreatitis.

Case 5 A male, aged 31 years, had suffered an attack of lumbago four years previously. Recently excruciating pain developed in the posterior aspect of his right

thigh and leg. The Lasague and Patrick signs were positive. The condition was diagnosed as acute sciatic neuritis.

The icterus index of the blood was 15 and the bilirubin content 0.6 mg per 100 c.c. (slightly elevated above normal). Ten days later these figures were still elevated. After a fortnight, the icterus index and the bilirubin content of the blood decreased to 8 and to 0.3 mg per 100 c.c. respectively (normal values). The blood cholesterol was 250 and later 235 mg per 100 c.c. The ester partition was normal. The urobilin content of a 24 hour specimen of urine was normal. Tyrosine⁸ was not demonstrable in the urine. The galactose tolerance test showed a normal result. The cinchophen oxidation test⁹ indicated moderate liver cell function impairment. On successive tests, 33.5, 33.0, 31.0 and finally 13.5 per cent of the test dose of 0.45 gram of cinchophen were excreted as oxy-cinchophen. Normal subjects excrete less than 21 per cent of this partial oxidation product in the urine after the test dose. The decrease in the latent jaundice, and in the oxy-cinchophen excretion occurred simultaneously with the subsidence of the pain. The patient was observed over a period of six weeks.

COMMENT

Liver function has rarely been studied in patients with sciatic neuritis. The levulose tolerance test was applied by Miller⁶ to 18 cases of sciatica with evidence of diminished tolerance in five. Eppinger⁷ noted liver function disturbance in five cases of polyneuritis and implicated a hepatic factor even in subjects with definite histories of lead and alcohol poisoning. I observed a marked spontaneous phenoluria or cresoluria in the urine of a female subject suffering from severe sciatic neuritis some years ago while studying tyrosinuria by means of the tyrosinase reaction. (The phenols and polyphenols give a pink reaction with this ferment, while tyrosine produces melanin, a brownish black, or violaceous pigment, specifically.) In the subject with sciatic neuritis reported above (case 5) the icterus index and the quantitative Van den Bergh reaction demonstrated a latent icterus. This subsided with the pain as did the liver function impairment recorded by the cinchophen oxidation test of liver cell function. Thus there is evidence that sciatic neuritis may be accompanied by subclinical hepatic damage.

An analgesic effect attributed to the jaundice was noted in some instances. The relief from pain was greater than could be expected from confinement to bed alone. The pain was noted to recur in one instance as recovery from liver injury took place (case 3). The possible analgesic influence of retained bile salts in jaundice was considered⁴ and the analgesic properties of bile salts were therefore tested experimentally. When introduced into the spinal canal of cats, an analgesic effect was not noted¹⁰. It is suggested that associated disturbances in mineral and water metabolism observed in acute liver degeneration may possibly contribute to the analgesia since some synthetic analgesics also alter water and electrolyte relationships of cells.

Careful interrogation has eliminated the possibility of cinchophen in any form in three of the cases of sciatica complicated by jaundice. In case 4 a single dose of cinchophen (5 grains) had been injected intravenously. In case 3 the patient, a physician, had taken novatophan, 18 years previously, for an attack of sciatica. For his recent recurrent sciatic pain this drug

was not used. In case 1 the only medication taken over a period of six months was ten grains of acetylsalicylic acid, despite excruciating sciatic pain. I doubt whether the ingestion of a single or a few doses of cinchophen in these two cases played any rôle in the causation of jaundice. The administration of single doses of this drug to patients with frank liver damage appears to have no ill effect.⁹ The possibility that liver injury may result from an idiosyncrasy to this drug in certain individuals with or without latent liver insufficiency cannot however be dismissed, but is unlikely in these two instances.

In the cases reported there was no history of alcohol abuse, or lead poisoning to account for the sciatic neuritis. No other nerves were involved. There was no clinical ground for suspecting a vitamin B₁ deficiency.

SUMMARY

Five cases are reported in which the symptoms of sciatic neuritis preceded the onset of clinical evidence of liver damage and jaundice. In three instances the jaundice and liver disease occurred in persons who had not ingested cinchophen in any form.

These observations suggest that endogenous toxic substances, responsible for the peripheral neuritis involving the sciatic nerve, may also be responsible for liver injury.

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THE RESPONSE TO THE FEEDING OF CEVITAMIC ACID IN NORMAL AND DEFICIENT SUBJECTS AS MEASURED BY A VITAMIN C EXCRETORY TEST*

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THE criterion for the diagnosis of scurvy had been, until recently, the appearance of the symptoms of scurvy. As a result of the experimental work in vitamin C, three new diagnostic procedures have now come into use: the capillary resistance test, the concentration of vitamin C in the blood and the urinary excretion of vitamin C^{1, 2, 3, 4, 5}. There is still some controversy as to the value of capillary resistance tests as an index of vitamin C deficiency. We have studied the capillary resistance of 25 young normal adults by the Dalldorf method⁵ and found no definite relation between vitamin C excretion, capillary resistance and diet. In this respect our findings agree with those of Anderson, Hawley and Stephens⁶. It is our impression that capillary resistance is influenced by several factors and although it is usually low in patients with scurvy, it is not as reliable an index of the degree of vitamin C deficiency as is the excretion of vitamin C or the blood vitamin C.

In this study the vitamin C excretory test, described in a preliminary report,⁷ was used not only to verify the diagnosis of scurvy and vitamin C subnutrition, but to study the response of such subjects to vitamin C therapy.

Procedure. Three groups were studied: a normal group of 12 young adults whose diet was adequate in vitamin C, a group of 3 normal subjects with no evidence of scurvy but whose diets were low in vitamin C and a third group of 22 patients with clinical evidence of scurvy.

The three hour excretion of vitamin C following the intravenous test dose of 100 mg of cevitic acid was determined in all three groups. In the normal and subnutrition groups the excretion of vitamin C was also determined for the total 24 hours. Following this, vitamin C as cevitic acid (Meck & Co) was fed to nine of the normal subjects, to the three subnutrition subjects and to all of the patients with scurvy.

In addition, to ascertain whether there was an advantage in using a larger test dose than the one originally advised (100 mg of cevitic acid), a group of normal and of scorbutic subjects were given an intravenous injection of 100 mg of cevitic acid and after an interval of two days an injection of 500 mg.

1 *In the Normal Subjects and in the Subjects on Diets Low in Vitamin C.* During the experimental period the subjects remained on their regular

* Received for publication July 30, 1937.

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diets, being careful to avoid any change in the intake of food high in the vitamin. The urines were collected as follows. The subject voided one to one and a half hours after breakfast. This specimen was discarded. The urine was then collected for the next three hour period and the vitamin C excretion determined. The urine was also collected for the following 21 hours. The next day, after voiding, the subject was given intravenously 100 mg of cevitic acid (Merck & Co.) and the urines were collected in the same way as before. Vitamin C feeding was then begun as cevitic acid 50 to 100 mg daily and the tests were repeated at intervals.

2 *In patients with scurvy* the same procedure was followed as in the normal subjects, with this difference that in the severe cases the cevitic acid was at first given intravenously and then in larger daily doses. When given by mouth, the cevitic acid was fed at 12 noon and 4 p.m. Cases 22 and 28 had received some orange juice prior to our original excretory determinations.

3 *Comparison of the 100 mg and 500 mg Test Doses on the per cent of the Vitamin Excreted in Three Hours*. In ten normal subjects intravenous test doses of both 100 and 500 mg of cevitic acid were given. An interval of two days elapsed between these two test doses, the 100 mg dose was given first. The urines were collected in the usual manner. This procedure was also carried out on eight patients with scurvy. In this study the urines were not collected for the 21 hours following the three hour test period.

4 *Method of Estimating Vitamin C in Urine and Blood*. Vitamin C was determined by titration against a standardized solution of 2,6-dichlorophenolindophenol by the method of Buch, Harris, and Ray.⁸ All necessary precautions were taken to insure against loss of the vitamin. The urines were acidified to 10 per cent of their volumes with glacial acetic acid. The three hour specimens were titrated immediately. Of the 21 hour specimens, those voided before supper were done immediately and the remaining specimens were collected in dark bottles in which there was a given amount of acetic acid and these were kept in the ice box. We have, as many other observers, studied the rate of destruction of the vitamin in urine and found that in acidified urine, kept in the cold, there is very little loss within 12 to 16 hours.⁹ It is also important that the urine in the bladder should be acid especially in patients with a low excretion of the vitamin.¹⁰ Where there was a tendency for the subject to excrete an alkaline urine, small doses of ammonium chloride were given. This was necessary in four cases.

Blood vitamin C was determined on 15 of the scurvy patients and on nine of the normals by the Farmer and Abt method.⁴

RESULTS

1 *Normals*. Table 1 gives the age, weight, height and capillary resistance of the normal subjects. The three hour excretion (Table 3) of vita-

TABLE I
Normal Subjects

Case No	Age Yrs	Weight lbs	Height in	Cap Res cm	Diet Rating
1	23	139	66	15 cm	3+
2	23	155	70	40 cm	3+
3	23	165	73	15 cm	3+
4	24	145	73	20 cm	2+
5	23	140	69	30 cm	2+
6	22	177	70	20 cm	3+
7	23	170	69	15 cm	3+
8	21	176	71	35 cm	3+
9	22	170	71		3+
10	23	143	67	15 cm	2+
11	25	168	70	30 cm	2+
12	20	155	70	40 cm	2+
13	21	170	71	20 cm	1+
14	25	150	69	40 cm	1+
15	21	170	72	20 cm	2+

1+ Signifies diet low in vitamin C
 2+ Signifies diet fair in vitamin C
 3+ Signifies diet high in vitamin C

min C in the normal subjects on diet alone varied from 4.5 to 25 mg, the average being 12 mg. The 21 hour excretion varied from 30 to 180 mg with an average of 67 mg. Following the intravenous injection of 100 mg of cevitamic acid the three hour excretion rose in all the normal subjects, the total excretion varying from 24 to 81.8 mg with an average excretion of 47 mg. The 21 hour excretion rose in four cases and fell or remained approximately the same in the rest of the group. The average 21 hour excretion was 67 mg. The intravenous test dose done after the feeding of 400 mg of cevitamic acid to nine of this group was followed by an increased excretion within three hours in five of the nine subjects. The average excretion in three hours for these nine subjects rose to 64 mg, and in the following 21 hours rose to 88 mg, thus raising the average 24 hours excretion to 152 mg. Continued feeding of cevitamic acid in six subjects further increased the three hour excretion after the intravenous test dose. The subject in whom no further increase was effected had originally excreted 81.8 mg of the 100 mg injected. Three of the subjects, after continued feeding of cevitamic acid, excreted more than 100 mg of vitamin C in the three hours after the test dose. Part of this was of course derived from the tissue stores and suggests a state of complete saturation.

2. *Subjects on Low Vitamin C Diets (Table 4)* On diet alone these subjects excreted an average of 1.9 mg in three hours and 10.2 mg in 21 hours, a total of 12 mg for 24 hours. The test dose caused a rise in the three hour excretion, but this was far below that seen in the normal subjects, the average being 10.4 mg. The following 21 hour excretion was not raised but actually was lower. After feeding 1000 mg of cevitamic acid, all three

Summary of Patients with Scurvy

Case No	Sex	Age	Duration of Deficient Diet	Other Complications	Clinical Signs of Vitamin C Deficiency							Capillary Resistance Cmm	Bld Vit C mg %	
					Referable to the Gums						Other Clinical Signs			
					Spongy	Piled Up	Bleeding	Ulcerated	Hem into Gums and Buccal Muc Memb	Massive Subcutaneous Hemorrhage	Presence of Petechiae Location			
20	M	40	3-4 mos	None	+	+	+	+	Massive	Into both legs	No	30	—	
21	M	68	12 mos	Art scl and hypertension	0	0	0	+	+	Both legs	Left leg	15	—	
22	F	38	3 mos	None	0	0	+	0	+	No	No	—	—	
23	F	22	3 mos	Malnutrition	+	+	+	0	0	No	No	20	0.35	
24	M	55	14 mos	None	+	+	+	0	0	Both legs and popliteal spaces	No	15	—	
25	M	21	14 mos	Possible rh fever	0	+	0	0	+	No	Legs and forearms	15	—	
26	F	76	12 mos	Art scl	0	0	0	0	0	No	No	18	0.23	
27	F	45	11 mos	Ulcer diet	0	+	+	0	0	No	No	10	0.0	
28	F	21	12 mos	None	0	+	+	0	0	No	No	—	1.3*	
29	M	60	3 mos	Strept hem	0	0	0	0	0	No	Both legs	5	0.55	
30	M	71	24 mos	Tuberculosis	0	+	0	0	0	No	Bleeding lips	—	0.0	
31	M	70	Intermittent for 3 years	None	0	+	0	+	+	No	Both legs	15	—	
32	M	56	12 mos	Alcoholism	0	0	+	0	0	No	Epistaxis	30	0.50	
33	F	42	4 mos	Profound malnutrition	0	0	0	0	0	No	Epistaxis	40	0.39	
34	F	52	24 mos	Lues and arthritis	0	+	0	+	0	0	No	—	0.52	
35	F	54	Undetermined	Hyperthyroid	0	0	0	0	0	No	Both arms	—	0.19	
36	M	70	On and off for 3 years	Art scl and hypertension	0	0	+	+	+	No	Lower arms	20	—	
37	F	49	3-4 mos	Fibromyoma of uterus	0	0	0	Slt	0	No	Colored patient	—	0.65†	
38	M	44	24 mos	Aneurysm aorta	0	+	0	0	0	No	Both arms	—	0.48	
39	F	47	Always poor	Diabetes and thrombophlebitis	0	+	0	0	0	Large purpuric spots	Arms, legs, face	30	0.35	
40	M	45	2 years	Coronary occl	0	+	+	+	0	No	Both arms	—	0.37	
41	F	45	5 years	None	+	+	0	Slt	0	No	No	—	0.59	

* Patient had been on orange juice daily for 6 days prior to this determination † Blood taken 2 hours after breakfast

TABLE III

Mg Vitamin C Excreted in Normals Following Injection of 100 Mg Intravenously, before and after Feeding Cevitamic Acid

Case No	Mg Excreted on Diet		Mg Excreted after Test Dose of 100 mg I V		Mg Excreted after 400 mg and Test Dose		Mg Excreted after 850 mg and Test Dose		Mg Excreted after 1800 mg and Test Dose		Mg Excreted after 2050 mg and Test Dose		Mg Excreted after 3000 mg and Test Dose	
	Hours		Hours		Hours		Hours		Hours		Hours		Hours	
	3	21	3	21	3	21	3	21	3	21	3	21	3	21
1	25.4	180.7	52.7	125.8	51.2	93.3	62.3	132			58.5	107	72	154
2	9.0	53.2	24.2	87.1	60.0	108.9			147.0	91.8				
3	16.8	81.6	81.8	73.8	107.7	76.1			86.0	184				
4	21.2	44.7	67.0	89.3	46.5	124.9			103.7	71				
5	8.5	109.0	40.5	104.0	38.7	137.3	41.8	128.3			113.0	87		
6	6.4	31.1	32.0	34.6	54.1	82.0	38.6	49.9			74.0	77		
7	10.9	36.1	57.8	65.7	56.7	41.0								
8	12.9	30.1	44.6	49.3	94.0	89.3								
9	4.9	39.7	43.5	25.1	73.9	40.1								
10	4.5	58.9	47.8	53.5										
11	12.1	51.9	37.6	47.9										
12	10.9	86.9	34.4	80.9										

TABLE IV

Mg Vitamin C Excreted in Normals on Diet Low in the Vitamin, after a Test Dose both before and after Feeding Cevitamic Acid

Case No	Mg Excreted on Diet		Mg Excreted after Test Dose		Mg Excreted on Test Dose after Feeding 1000 mg		Mg Excreted on Test Dose after 1500 mg		Mg Excreted on Test Dose after 2000 mg	
	Hours		Hours		Hours		Hours		Hours	
	3	21	3	21	3	21	3	21	3	21
13	1.4	9.5	11.5	4.8	52.8	39			57.9	60.8
14	2.2	11.7	5.6	1.6	44.1	39	67.2	65.9		
15	2.3	9.5	14.2	9.1	36.2	20.6			53.3	22.5
14*			2.7		17.1†		38.5			

* Second study after an interval of 3 months

† Amount of cevitic acid fed at the time of this test was 650 mg

subjects excreted more than 36 mg of the injected vitamin, the average being 44 mg. The 21 hour excretion rose, but was not as high as the average excretion in the normals on diet alone. Continued feeding of cevitic acid caused an increase in the three hour excretion following the test dose and the 21 hour excretion rose in two of the subjects. Case 14 was studied a second time after an interval of three months, during which time he had received no cevitic acid. The excretory test was again low, 2.8

mg After feeding 650 mg of cevitic acid, the excretion after the test dose rose to 17 mg and after feeding 1500 mg, 38.5 mg were excreted

3 *Patients with Scurvy* (A) *Symptoms* Table 2 summarizes the symptoms and signs of vitamin C deficiency observed in the 22 cases studied. Only six cases were uncomplicated. Malnutrition was profound in two cases. Arteriosclerosis in varying degrees was present in four cases. Symptoms referable to the gums were found in 16 cases. These varied considerably, but definite piling up of the gums with retraction from the teeth was present in 13 cases. Hemorrhage or petechiae or both were found in 15 patients. The capillary resistance done in 13 cases was low in nine. The blood vitamin C, done in 15 cases, was below 0.55 mg in twelve. In one case, number 28, the patient had had orange juice for one week before the study and the blood vitamin C was normal.

(B) *Excretion in Patients with Scurvy* (Table 5) These patients were on the wards of the Third (New York University) Medical Division, Bellevue Hospital. Cases 22, 28 and 41 were studied in the Metabolism Clinic of the College of Medicine Clinic, New York University. Case 26 was studied twice, once in the clinic and later in the hospital. Prior to the administration of vitamin C, the average three hour excretion in the scurvy patients was 1.4 mg. In some cases no vitamin C was titratable in the urine, in four cases it was less than 1 mg. The 21 hour excretion averaged 6 mg. After the 100 mg test dose of cevitic acid, the average three hour excretion was 2.5 mg. The 21 hour rose to an average of 10 mg. In cases 20, 21, 29, 30, 31, 39 and 41 cevitic acid was given intravenously until clinical improvement was noted and then by mouth. The tests were repeated at frequent intervals after the feeding of the vitamin and in six cases (23, 26, 27, 31, 32, and 36), the excretion was followed daily during the patient's stay in the hospital. The other patients were followed at weekly or semi-weekly intervals. In five cases (33, 34, 35, 37 and 38) although cevitic acid was administered, excretory tests were done only after the test dose. In table 5 the excretory tests following the administration of cevitic acid are reported. As it would require too much space to report every case in detail, this table summarizes the results at intervals during the studies.¹ In those cases where the excretion was determined daily, it was found that the excretion remained low for from 4 to 12 days and then approached the normal. The amount of cevitic acid required to bring the excretion to the normal level depended on the duration of the deficient diet and the presence of complicating conditions.

4 *Comparison of 100 mg and 500 mg in Test Doses of Cevitic Acid on the Three Hour Excretory Test* Ten of the normal subjects (1, 3, 4, 5, 6, 7, 8, 10, 12, 13 and 15) were given intravenous test doses of 100 mg of cevitic acid and two days later 500 mg. These tests were carried out three months after the original studies were completed. The normals excreted an average of 53.8 per cent in three hours after the 100 mg test dose and 55.8 per cent after the 500 mg test dose. Undoubtedly the higher

excretion within three hours represents a higher dietary intake of vitamin C. These normal subjects had become vitamin C conscious as a result of these studies and almost all had increased their daily intake. Eight patients with clinical signs of scurvy were similarly tested. The average three hour excretion after the 100 mg dose was 1.6 per cent, after 500 mg, 7 per cent.

The results on the normal subjects show that there is no particular advantage in using the larger test dose of cevitamic acid. In the patients with scurvy, apparently the per cent excretion is somewhat higher following the larger dose. If such a dose were to be used, it would merely require establishing the limits of the three hour excretion. We feel, however, that as

TABLE V

Vitamin C Excretion in Patients with Scurvy as Measured by Test Dose before and after Feeding Cevitamic Acid

Case No	Mg Vitamin C Excreted on Admission		Mg Vitamin C Excreted after Test Dose before Feeding Cevitamic Acid		Effect of Feeding Cevitamic Acid on 3 hr Excretion Following Test Dose		Remarks
	3 hr	21 hr	3 hr	21 hr	Mg Fed	Mg Excreted	
20	3.3		3.6		1400 4550 6100	15.5 57 86	Given intravenously up to 3600 mg
21	2.2		1.3	4.7	800 2200 4000	1.4 3.3 8.0	Given intravenously up to 3300 mg
22	not	done	7.9*		2500	34	*Had taken orange juice for 1 week before tests. Cevitamic acid given orally
23	2.1	8.2	3.9	12.9	2700	95	Cevitamic acid given orally
24	0		0		2000	0	Cevitamic acid given orally—never excreted any in urine but symptoms cleared
25	2.0	6.2	Tr	0			Left hospital
26-1	0.4	3.0	0.5		1100 2600	16.5 33.2	First study done in clinic. Cevitamic acid always given orally
26-2	0.7	1.5	0.3		2600	32.0	2nd study after interval of 6 weeks with no cevitamic acid
27	0.3	0	1.0	0	2000 6660	28.3 59.2	Cevitamic acid given orally
28	0.2		9.7	23.9	900 1700	19.0 70.8	Clinic pt. had taken orange juice for 1 week before tests. Cevitamic acid given orally

TABLE V—*Continued*

Case No	Mg Vitamin C Excreted on Admission		Mg Vitamin C Excreted after Test Dose before Feeding Cevitamic Acid		Effect of Feeding Cevitamic Acid on 3 hr Excretion Following Test Dose		Remarks
	3 hr	21 hr	3 hr	21 hr	Mg Fed	Mg Excreted	
29	2 0		4 7	14 1	400 800	3 3 1 7	Cevitamic acid 500 mg intravenously
30		0 8	1 8	21 5	1200	5 9	Cevitamic acid given intravenously
31		0	0 4	1 5	1500 4200 6700	0 9 45 55	3300 mg ceviticamic acid given intravenously, after this, orally
32	0 7	5 2	2 3	6 6	1500 3400 5900	15 45 48	Cevitamic acid all given orally
36	0 7	2 0	0 5	1 83	1500	0 3	Cevitamic acid given orally
39			1 4		1200 3100 4600 5600 6700	2 9 3 5 7 7 14 30	1500 mg of total amount of ceviticamic acid were given intravenously Pt a diabetic
40			1 6		1500 2300 4000 6700	3 9 3 3 3 7 25 0	Pt had coronary occlusion Cevitamic acid by mouth
41			2 4	8 1	4600 8600	32 0 50 0	600 mg intravenously, then orally

the smaller test dose gives consistent and accurate results, it is preferable to a larger one because in following the excretory response to vitamin C therapy, there is less chance of saturating the patient when the smaller dose is used

DISCUSSION

From these studies it is obvious that normal young adults on a presumably normal diet will excrete varying amounts of vitamin C daily. The question arises as to what constitutes a normal excretion. From our results and the results of other investigators¹⁻³ there is apparently a rather wide range of excretion in the normal which is naturally influenced by diet. In view of the difficulties of collecting 24 hour urine specimens and of protecting against loss of the vitamin in urines collected over a long period of time, we have attempted to evaluate the significance of the excretion for a three hour period after an intravenous test dose of ceviticamic acid. The three hour ex-

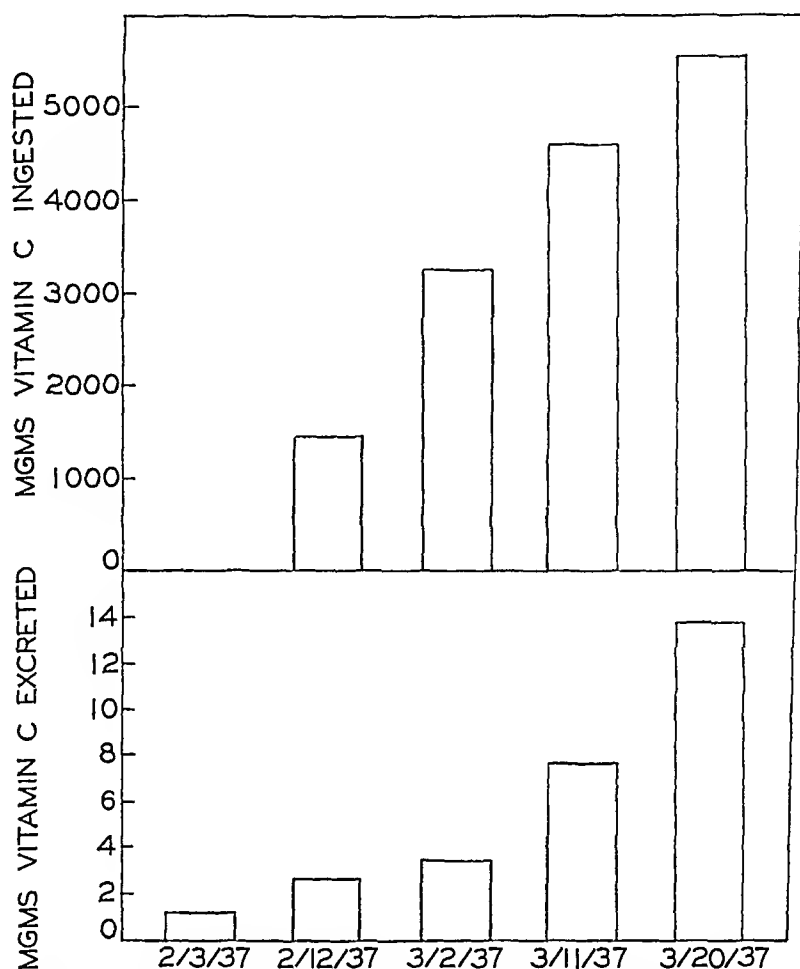


FIG 1 Case 39 The three hour excretion tests before and after the administration of cevitamic acid

cretion on diet alone may be fairly low in normal individuals. If, however, one studies the three hour excretion following an intravenous test dose of 100 mg of cevitamic acid, the difference in excretion between normal subjects, scorbutic subjects and subjects on a low vitamin C diet is quite definite. Of the 12 normal subjects studied prior to feeding any additional vitamin C, 11 excreted more than 32 per cent of the injected vitamin in three hours. Of the three subnutrition subjects all excreted less than 15 per cent in three hours and in the subjects with scurvy, excluding cases 22 and 28 who had been receiving orange juice prior to the original test, all excreted less than 5 per cent in three hours. These results were consistent with the 24 hour excretion. It seems reasonable, therefore, to suggest that the excretion of vitamin C following an intravenous test dose of 100 mg can serve as an index of whether or not the subject is deficient in vitamin C.

The results of feeding vitamin C to these three groups of patients bring out the fact that the normal subjects excreting less than 80 per cent of the

injected vitamin in three hours can be stimulated to excrete larger amounts following the feeding of vitamin C. One may infer that when more than 70 per cent of the injected vitamin is excreted in three hours, the tissues of the individual are well saturated with the vitamin. This does not mean, however, that complete saturation of the tissues is necessary in an individual in order to have a normal state of vitamin C nutrition.

The subjects on the low vitamin C diets responded very promptly to the feeding of vitamin C and their three hour excretion reached the normal level after the feeding of 1000 mg of cevitic acid. In this respect they show again the difference between subnutrition and absolute deficiency of vitamin C. The scorbutic patients required much larger doses before their three hour excretion test fell within a normal range. In fact in some instances this did not occur during the period of these observations.

The diets of the subnutrition cases are the ones of most interest in the field of nutrition. The three subjects studied were medical students and their diets were low in fresh fruit and in uncooked vegetables. Practically none of these men took any oranges and only occasionally an apple. Their response to the feeding of cevitic acid suggests that their tissue reserves of the vitamin were low, but apparently had not reached the stage where any demonstrable clinical or pathological effect could be found. The capillary resistance in two of these subjects was 20 cm and was 40 cm in the third subject. It is quite likely that pathological changes in the tissues as a result of vitamin C deficiency do not occur until an absolute state of deficiency has existed for some time. Youmans and his associates¹¹ found that of 15 subjects whose diets were inadequate in vitamin C, 12 excreted less than 20 mg of the vitamin in the urine daily. The 24 hour excretions in our subnutrition group substantiate these findings.

Of the 22 cases showing symptoms of scurvy, only six cases were uncomplicated by other diseases. This brings up the fact that vitamin C deficiency is probably seldom uncomplicated and that other pathological states may increase the vitamin C requirement of the individual. Administration of cevitic acid improved the clinical symptoms in all cases, in several cases this improvement was apparent before the excretory test had reached the normal level.

SUMMARY

1 The three hour urinary excretion of vitamin C before and after an intravenous test dose of 100 mg of cevitic acid was studied in a group of 12 normal adults, 3 normal individuals on diets low in vitamin C and 22 cases of scurvy.

2 The three and 21 hour excretion was studied in the same group after an intravenous test dose of 100 mg of cevitic acid and the intravenous test dose was repeated in all three groups following the feeding of cevitic acid.

3 Following the intravenous test dose the 12 normal subjects excreted an average of more than 40 per cent of the injected vitamin within three hours. The extremes were 24 to 82 mg. The three subnutrition cases excreted 5 to 14 mg. The cases with scurvy excreted from 0 to 5 mg.

4 Following the feeding of 1000 mg. of cevitamic acid to the subnutrition subjects, the three hour excretion rose to the normal level after the test dose. In order to increase the urinary excretion to the normal level in the patients with scurvy much larger amounts of the vitamin had to be fed. In the normal group the feeding of cevitamic acid in small doses increased the vitamin C excretion above the original level.

5 Excretion tests were also done following an intravenous test dose of 500 mg. of cevitamic acid in normal and scorbutic subjects. The normals excreted an average of 55.8 per cent, the scorbutic patients an average of 7 per cent of the injected vitamin.

6 As a result of these observations it is suggested that the urinary excretion of vitamin C following an intravenous test dose of 100 mg. of cevitamic acid will serve as an index of vitamin C deficiency or subnutrition and as a guide to show the degree of saturation of the tissues following the feeding of cevitamic acid.

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PEPTIC ULCER THE EFFECT OF THE ADMINISTRATION OF BILE ON THE BEHAVIOR OF THE DISEASE ^

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Two reasons prompted us to administer bile to patients with peptic ulcer the evidence from experiments with animals that ulceration of the stomach or duodenum may follow the diversion of bile from the duodenum, and certain other evidence which suggests that the disease may result from some type of deficiency

Numerous studies have been reported in which ulceration has developed after interference with the normal secretions in the duodenum A review of the literature on this subject has been published by us in two previous articles ^{1, 2} and will not be repeated here Briefly, the various experimental methods that have been most successful in producing peptic ulcerations in animals, usually dogs, have involved side-tracking or shutting off the flow of bile or pancreatic juice to the duodenum, or damaging the liver, as by chemical poisons, cinchophen, etc These studies may be divided into three groups

(1) Experiments which have severed the duodenum from the stomach, and in this way prevented a normal mixing of hydrochloric acid with the duodenal secretions, succus entericus, bile and pancreatic juice

(2) Experiments which have diverted only one of these three secretions

(3) Experiments which have caused damage to the liver

In addition, there have been observations, both in animals and in man, of spontaneous ulceration in association with a diseased liver

The experimental work included under groups 1 and 2 was inspired by the conception that ulcer might be the result of a defect in the process of neutralization of the gastric juice by regurgitated alkaline duodenal contents The results of this work support the contention that unneutralized hydrochloric acid can damage the mucous membrane However, it is difficult to apply the interpretation of these results to an explanation of the cause of ulcer in man One cannot consider the damaging effect of the acid without considering the resistance of the mucous membrane to that effect Indeed, most investigators have felt that trauma and the resistance of the mucous membrane are important factors in determining whether these experimental ulcers develop As these complex experiments were carried on, it was found that tying off either the biliary or pancreatic ducts might be followed by the development of an ulcer A question then naturally arose as to which was

* Received for publication May 21, 1937

From The Medical Clinic of the Peter Bent Brigham Hospital

the more important of the two. On this question various observers have disagreed. Ivy and Fauley,³ Elman and Hartman⁴ have found a high incidence of ulcer formation in animals following interference with the normal flow of pancreatic juice into the duodenum. Conversely, Kapsinow,⁵ Weiss and Hubster,⁶ Berg and Jobling,⁷ Bollman and Mann,⁸ and others have found a higher percentage of ulcer formation following interference with the normal flow of bile. Berg and Zucker,⁹ and Berg¹⁰ comparing the frequency with which ulcers followed the diversion of bile or pancreatic juice found the greater incidence of ulcer formation after the exclusion of bile.

The evidence at present suggests that the loss of bile is the more important of the two. Strengthening this idea is the recent work reported by Blanck¹¹ in which ulcers developed in five of eight dogs after the complete external drainage of bile. Moreover, he claims to have prevented the development of ulcerous lesions in three other dogs similarly treated by refeeding the bile drained off. It is unfortunate that after the lesions developed, he did not attempt to bring about their healing by the administration of bile. It is evident that the lack of either bile or pancreatic juice in the duodenum, or the loss of these substances will frequently result in the formation of an ulcer in experimental animals. But, the explanation that these lesions are the result of an inadequate neutralization of the gastric juice seems to rest on insecure evidence. Certainly, this explanation cannot easily be applied to the behavior of ulcer in man.

Our present knowledge about peptic ulcer logically divides our theories on its etiology into two groups: (1) that peptic ulcer is due to the destructive effect of hydrochloric acid on a normal mucous membrane, or (2) that the disease results from a local decreased resistance of the tissues to peptic activity of the gastric juice. There is undoubted evidence, both experimental and clinical, that peptic activity plays a role in the development of ulcerous lesions (Mann and Williamson,¹² Matthews and Dragstedt,¹³ Lindau,¹⁴ and others). However, there is no evidence that it is the sole cause of the lesion. If the ulcer is associated with the hydrochloric acid, changes in the activity of the ulcer must be associated with a change either in the acid, or in the resistance of the tissues to the damaging or corrosive effect of that acid. There is no evidence that the quality of the human gastric juice varies with a change in the state of the ulcer which would seem inevitable if the destructive effect of the juice were the important factor in the development of the lesion. Recently, Schnitker and Evans¹⁵ have reported that there is no change in the quality or quantity of human gastric juice from the period of a preulcerous state to the time when an active lesion could be demonstrated. Moreover, there are a sufficient number of cases of ulcer with low acid values to make it seem probable that peptic ulcer in man depends upon something other than, or in addition to, the destructive effect of the hydrochloric acid. The progressive susceptibility of the lower intestine to the corrosive effect of the gastric juice suggests the importance of

the normal resistance of the tissues to this damaging influence. Also, it is difficult to believe that the factor of safety in the mechanism for neutralization of the hydrochloric acid is so slight that a diversion of either one of the alkaline juices is sufficient to leave the duodenal mucous membrane unprotected.

The other theories, such as the neurogenic, vascular, and infectious fall into the second group, implying a decreased tissue resistance. These theories are based more upon clinical observation than upon experimental work. The experimental ulcers which most resemble those found in man have been produced only by technics similar to or related to the Mann-Williamson operation. This does not lend support to the neurogenic, vascular, or infectious theories.

That a deficiency of some kind may be the cause of ulcer is a possibility which has received little attention, although there is much in the behavior of the disease to make tenable such an hypothesis. The clinical behavior of the disease is comparable in many ways to that of pernicious anemia, which is also chronic, passing through alternating cycles of activity and quiescence, and being influenced by emotion, fatigue, and infection, similarly to ulcer. All the experimental work based on the operative principle stressed by Mann and Williamson, of necessity interferes with the normal physiology of the gastrointestinal tract. There has not been excluded the possibility that the formation of ulcer may depend upon a disturbance in digestion which results in a deficiency. The fact that a diversion of any of the secretions found in the duodenum will produce an ulcer, favors the idea that a disturbance in digestion is the cause of the disorder as much as, if not more, than it favors the theory of failure in neutralization of the gastric juice as a causative factor. Supporting this idea of "deficiency" are the studies carried out by McClure and Huntsinger¹⁶ in which they found that in 8 of 12 patients with symptoms of an uncomplicated duodenal ulcer, the biliary fraction was "decidedly abnormal," particularly with respect to the bile acids.

In summary, therefore, we have been led to administer bile to patients with peptic ulcer because of the reports in the literature of instances in which lesions of the gastric or duodenal mucosa have been associated both in animals and in man with interferences with the normal flow of bile into the duodenum, because the absence of bile seems to be more important than loss of pancreatic juice in the formation of ulcer, because peptic ulcer may be considered a type of "deficiency" disorder in which a loss of the protective mechanism of the duodenal mucosa allows ulcers to develop, and, because studies of the bile have shown an abnormality in cases of duodenal ulcer.

The administration of bile to patients with gastric complaints, or even peptic ulcer, is not new, although at the present time there is much more experimental and clinical data to suggest and warrant its use than was available to the previous experimenters. About 1913, Palfrey¹⁷ in this country, and Glacssner¹⁸ in Germany discussed the treatment of peptic

ulcer with the use of bile. Both writers reported symptomatic improvement in their cases. Jarno¹⁹ in 1926 and Thom²⁰ in 1932 have also discussed the effect on patients of a preparation called "salvacid." According to Thom this preparation contains *fel tauri sicca*, *Thujoncholyglyzin*, acetylglycocholic acid, together with calcium carbonate and sodium bicarbonate.

OBSERVATIONS

Based on these considerations we began the administration of desiccated ox bile to patients with peptic ulcer in January 1934 and continued its use over a period of two years. We wished to use a product of bile which would be convenient to give and at the same time would be as similar to fresh bile as possible. Because the moderately high temperature to which the usual preparations of bile are subjected might change the quality of its ingredients, we asked the Burroughs and Wellcome Company for suggestions to overcome this difficulty. After some study their laboratory found that by mixing the bile with exhausted licorice root one could dry the preparation at a temperature below 38 degrees centigrade. They gave us enough of this material to carry out the study reported herein. We should like to take this opportunity to express our appreciation of the cooperation and many courtesies extended by the various members of the company.

The bile was enclosed in gelatin capsules containing 0.3 gram, 0.5 gram, and 0.75 gram. The larger capsules proved unsatisfactory because some of the patients found them difficult to swallow. Ultimately, we used only the 0.3 gram capsules.

It was difficult to know how much bile should be given in treating these patients. As previously stated, if peptic ulcer depends upon a disturbance in the biliary secretions, this disturbance may be in the nature of a quantitative or of a qualitative abnormality. Except for the work of McClure and Huntsinger, which suggests that a qualitative difference occurs in the bile of patients with ulcer, there is little information on the subject. We had no other choice than to give as much as a patient could tolerate. Before beginning the treatment of patients with ulcer, we determined the amount of bile that could be tolerated by individuals with no gastrointestinal disease. Eighteen such patients who were on the medical wards of the Peter Bent Brigham Hospital were given increasing amounts of bile. It was found that individual patients varied in the amount which they could tolerate. On the average these persons could take 3.0 grams of our material a day if given in divided doses. A few were able to tolerate 4.0 grams but some were upset by 2.5 grams. The ill-effects consisted of anorexia, nausea and slight diarrhea. Occasionally a patient complained of slight epigastric burning. We utilized these data to establish an upper limit of dosage of 3.0 grams per day in our patients with ulcer, and attempted whenever possible to give this maximum amount. Nearly all the patients were able to take

daily a dosage of two capsules of 0.3 gram of bile every two hours for five doses

Altogether we have treated 40 patients with peptic ulcer. As established by the roentgen-ray, four had gastric ulcers, 32 had duodenal ulcers, and four had both. All the patients were seen and followed in the gastrointestinal clinic of the out-door department of this hospital, and except for one or two instances, they were ambulatory throughout the course of treatment. The duration of symptoms varied from 1 month to 25 years, with an average of 5.7 years. Ten of the group had received no previous treatment, whereas the others had been given various types of ulcer therapy. We endeavored to limit the treatment to therapy with bile only, but this was not always possible. Based on this fact, the 40 cases have been divided into two groups: (1) those whose therapy consisted of bile only, and (2) those who received some alkaline treatment in addition to the bile. Both groups were given a normal diet. It seemed wise to give these patients some kind of menu in order to guard against foolish excesses. Having used this diet for many years, we know that it will not of itself control the symptoms of ulcer.

A few patients complained of epigastric burning shortly after the ingestion of a capsule. We found this could be eliminated by the use of a full glass of water at the time the capsules were taken.

Group 1—Patients Treated with Bile Alone There were 23 patients who were treated with bile alone. These individuals had had symptoms of ulcer from 1 to 22 years, with an average of 4.5 years. The duration of treatment varied from one week to two years (average 6.18 mos.), depending upon the results and the degree of cooperation obtained. The treatment in all instances was continuous. None of the patients was treated longer than two years. The results have been classified into four groups. The first consists of seven patients who had "excellent" results (Followed for an average of $7\frac{1}{2}$ mos.). These individuals were promptly relieved of all symptoms and continued to be free from complaints throughout the course of their treatment with bile. The second group comprises seven cases that had "good" results, with definite amelioration of their discomfort, they did have, from time to time, mild symptoms that could be recognized as coming from the ulcer. (This group was followed for an average of $7\frac{1}{4}$ mos.) In the third group were three patients who had "fair" results, that is, they had less trouble than before the treatment was begun, but the results were not satisfactory from the point of view of either the patient or ourselves. (These were followed for an average of $6\frac{1}{2}$ mos.) In the fourth group were six patients who are classified as "failures" in that they did not receive any benefit whatever. Some of these refused to follow the treatment long enough for us to judge whether they would have received any improvement if the treatment had been continued longer. (These were followed for an average of $2\frac{3}{4}$ mos.)

As in all chronic diseases, the evaluation of the effect of therapy is very difficult in peptic ulcer. Our results would imply that bile is not a specific cure for the disease. However, as we followed these cases, the results were so striking in certain individuals that they seemed worthy of a careful analysis. The first thought which occurred to us was that the difference in results might be due to psychotherapy, a most important factor in the institution of any new form of treatment. We tried to avoid enthusiastic suggestions as much as possible. In addition, we attempted to classify these patients according to temperaments, without finding any striking differences in the groups. We could not convince ourselves that the difference in results could be explained on this basis, and, if a psychic influence played a rôle, we were not able to detect it.

The factor of previous therapy for the ulcer was considered next as of possible significance. Of the seven patients who had "excellent" results, six had received no previous kind of treatment. From the seven with "good" results, three had had no previous ulcer therapy. The nine patients who had only "fair" results or had failed to receive any benefit, had all had some kind of other treatment for the ulcer. This would suggest that the opportunity to compare the effectiveness of two kinds of treatment tended to make the patients with the previous therapy less satisfied with the bile treatment. Possibly, these patients were more than normally resistant to any form of treatment.

An attempt to correlate the results with the severity of the process has not been enlightening.

The range of acidity as determined by gastric analysis in the four groups was surprisingly constant. The average for the highest acidities was as follows:

"Excellent"	Free Acid	44°—	Total Acid	55°
"Good"	" "	49°—	" "	65°
"Fair"	" "	42°—	" "	58°
"Failures"	" "	53°—	" "	67°

The incidence of night pain, which is thought by many to be an index of secretion, was the same in the four groups.

Gastric analyses were obtained before and after the therapy in nine patients of this group who had been treated with bile alone. It is of interest, although its significance is not clear, that the gastric acidity was greater in all but two of these patients after they had received bile for some time. This was true of three patients who had "excellent" results, as well as of the others.

Other comparative studies do not show any essential difference in the relative severity of the disease in patients who had poor results and in those who had satisfactory results. The duration of symptoms before the treatment with bile was essentially the same in all groups, an average of about 4.5 years. The incidence of such complicating symptoms as nausea, vomit-

ing, and bleeding, was likewise similar in the various groups. The only observation that might suggest a difference in severity was the incidence of seasonal attacks. Six of the seven patients who had "excellent" results had definite seasonal attacks of pain, and under bile therapy these patients went without symptoms through the time of year when they expected an attack. Five of the seven who had "good" results had seasonal attacks of pain and four of the five were carried through successfully with bile. In contrast to this, only two of the nine patients who had poor results with the bile treatment had a seasonal occurrence of ulcer symptoms and neither of these two was relieved. The incidence of seasonal occurrence of symptoms, then, is the most striking difference between the patients who received satisfactory results and those who did not. We are not prepared to say on what this difference rests.

Group 2—Patients Treated With Bile Together With Some Alkali

There were 17 patients who received an alkaline Sippy powder (calcium carbonate 0.6 gram, sodium bicarbonate 2.0 grams) after each meal, in other words, three powders a day, in addition to the bile capsules. Some of them also took a half glass of milk and cream once between meals, that is twice a day. It seems necessary to discuss these patients in a separate group because they were receiving more than one type of therapy and for that reason the results were more difficult to evaluate. The additional powders were given in most instances because the bile was not giving complete relief of symptoms, or because a few requested them from fear that ulcer symptoms might return. The milk was given to those few who requested it inasmuch as they liked the habit of a forenoon and afternoon drink.

This group was followed from 1 to 12 months (average 6.2 months). The length of observation was correlated to some degree with the response to therapy. On the whole these cases did not do as well as those on bile alone. However, we have classified them under the same criteria as the group treated with bile only.

(1) Two patients had "excellent" results over a period of 10.5 months observation. (2) Five patients had "good" results over an average period of eight months. (3) Six patients had "fair" results over a similar period of observation, and (4) Four patients were "failures" remaining under treatment only six to eight weeks.

Reasons for the difference in results in this group were as difficult to detect as in those who received bile alone. The duration of symptoms before treatment was as follows: "excellent"—6 years, "good"—6 years, "fair"—5.5 years, "failure"—12.5 years. The average for the group is about 7.5 years. All but one of these patients had received a previous treatment for ulcer, the one exception fell into the group of "failures." The difference in results in this instance cannot be attributed to a comparison between the effectiveness of bile and the previous type of therapy.

An attempt to estimate the emotional and nervous reactions of the patients in this group casts no light upon the difference in results. The gastric analyses showed similar findings with the exception of the "fair" group, in which the acid values were distinctly lower. The average acid values of gastric juice for these patients were as follows:

"excellent"	Free Acid	67°—	Total Acid	70°
"good"	"	64°—	"	111°
"fair"	"	29°—	"	45°
"failure"	"	66°—	"	82°

It is striking how similar these figures are to those in Group 1. Five patients in this group treated with bile plus small amounts of alkali had gastric analyses done before and after the treatment, without, in this instance, any essential change in the values.

Thirteen of these 17 patients had a distinct history of seasonal ulcer distress of which eight were carried through this period without symptoms. It is striking that the four patients in whom treatment failed in this group had seasonal attacks of symptoms, as opposed to the failures in Group 1 in which only two of nine cases with poor results gave a seasonal history, the other seven having continuous symptoms.

No difference could be elicited between the results on the basis of the type of symptoms from which the patient suffered. The incidence of night pain was about the same in each class and this was true also of the incidence of bleeding.

DISCUSSION

It may be stated as almost an axiom, and certainly as an impression from observations, that *one can feed patients with ulcer disease almost anything and a certain number will respond favorably*. The literature reports good results from numerous and diverse methods of treatment. These good results may be explained by the fact, as pointed out by Emery and Monroe,²¹ that a spontaneous alleviation of symptoms may extend over a long period of time in as many as 48 per cent of individuals with ulcer. Because the symptoms are easily controlled, in most instances, there is only one criterion on which to judge results. That is the prevention of a relapse. Unfortunately, we have no other method of judging the effectiveness of therapy in this disease, as we have in pernicious anemia, in which the increased number of reticulocytes is an index of the response to treatment.

From the results obtained in the treatment of these 40 patients with peptic ulcer, we must conclude that desiccated ox bile is not a specific cure for the disease. A satisfactory result occurred in only 52.5 per cent which is not much better than can occur spontaneously. This seems to rule out a disturbance in the biliary secretion as a cause of peptic ulcer in man.

However, it is our impression that the administration of bile will relieve symptoms in a definite number of patients, and this impression was

strengthened by the prevention of a seasonal recurrence in 73 per cent of the patients. The mechanism of the favorable effect is not clear. It does not seem probable that the buffering effect of only 0.3 to 0.6 gram of bile in a dose would be sufficient to explain the relief. This is supported by observations made on two cases in which aspiration of stomach contents was done shortly after the ingestion of a capsule of bile. In neither instance was there noticed an appreciable effect on the gastric acidity. Furthermore, in none of the cases, whether the responses were good or not, was there a reduction in the values of free and total acid in the gastric analyses. In fact, some of the cases with "excellent" results in Group 1 had higher values in the gastric analyses after the period of observation with bile than before, although they had suffered no symptoms. These observations forced us to conclude that the beneficial results obtained with this form of treatment were probably not due to lowering of the gastric acidity.

It is a common observation that many patients with peptic ulcer tend to have constipation. The alleviation of this symptom by the bile treatment was observed and reported spontaneously by many of the patients. Upon questioning the others who had not expressed themselves, we found that all of them had more regular bowel habits as a result of the treatment, many being relieved of a cathartic habit. Only one patient developed any symptoms comparable to those experienced by the control cases when we established the dosage of the material. Only one other individual developed diarrhea at any time, and it was promptly relieved by a slight reduction in the dose and the patient continued free of ulcer symptoms. We have found that the ability of bile to relieve symptoms is useful in those patients who have kidney disease or renal calculi in addition to an ulcer, in whom one may hesitate to push alkaline therapy. There were two patients in this series from whom renal calculi had been removed. Both patients were given only bile. They both responded very well and remained free of ulcer distress for over a year during which they have been followed.

We have pointed out previously¹⁵ that there is no necessary correlation between the pain of ulcer disease and the roentgen-ray demonstration of a crater. This is again illustrated by three of the patients in Group 1 who were treated with bile alone. All three had responded well to the treatment. Some six to eight months after the initial roentgen-ray demonstration of a crater in the duodenum and the institution of bile therapy, repeat gastrointestinal studies were carried out. Although these three patients had been free from ulcer symptoms for these months, barium studies revealed a crater still present. Subsequent observation and studies have adequately shown that these were not instances of carcinoma.

Although bile was administered to these patients in order to learn its effect on the disease of ulcer, certain other observations were made. With the present universal interest in the study of hypertension and of means for its treatment, bile therapy too has been suggested -- as a method of lowering the blood pressure. We observed the blood pressure in six patients with

hypertension The ingestion of 20 to 30 grams daily of our preparation caused no changes in the blood pressure level that could not be accounted for by the normal daily variations There was no lowering of blood pressure in a few cases without hypertension

It has been reported^{23, 24} that perhaps an excess of bilirubin in the circulation or an increased amount of bile salts in the blood, or both, accounts for the analgesic effect of jaundice on the symptoms of arthritis Because of this observation, Sidel and Abrams have given bile salts to patients with arthritis with some gratifying results We had under observation for ulcer, one patient who had a moderate degree of infectious arthritis, to whom we gave the bile therapy His ulcer symptoms responded fairly well but his joint pains remained unchanged

SUMMARY AND CONCLUSIONS

Experimental peptic ulcers in animals which appear similar to those occurring in man have followed interference with the flow of bile into the duodenum or damage to the liver In man, ulcers have been observed associated with liver disease, and in a few instances qualitative abnormalities in the bile have been reported in cases of duodenal ulcer These facts, plus the hypothesis that a deficiency may be the important factor in the disease of ulcer, prompted us to administer desiccated ox bile to patients with peptic ulcer

A total of 40 patients with ulcer has been treated with bile over periods as long as two years Four patients had gastric ulcers, 32 had duodenal lesions, and four had both The 40 cases were divided into two groups (1) 23 patients who were treated with bile only, and (2) 17 patients who received some alkaline treatment in addition to the bile

The results from this treatment were as follows Nine patients (22 per cent) had "excellent" results, 12 patients (30 per cent) had "good" results, 9 patients (22 per cent) had "fair" results, and 10 patients (25 per cent) were "failures" These figures are such as to exclude desiccated ox bile as a specific cure for the disease However, bile may be useful as a means of relieving the symptoms of certain patients, in whom the use of alkalis is contraindicated

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EXERCISE TESTS AND THE ELECTROCARDIOGRAPH IN THE STUDY OF ANGINA PECTORIS¹

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DESPITE the high incidence of angina pectoris² and its varied causes, a relatively large number of patients, after most careful routine physical examination, roentgenological investigations, and routine electrocardiographic studies (including chest leads) yield findings within normal or nearly normal limits. In such cases the diagnosis must be made upon the description of symptoms obtained from the patient. According to Burnett¹ one-third of the patients, and according to the experience of Paul D. White² 20 to 25 per cent of the patients having angina pectoris fall within this group.

In many instances the history is so typical that a diagnosis of angina pectoris may be made with fair certainty in spite of the absence of objective findings. However, where the physician is confronted with the possibility of such a serious clinical entity, and especially where anxiety, fear, or suggestion are confusing factors, the desirability of objective evidence will be readily admitted. Such information is also important where atypical symptoms confuse the diagnosis. In addition to pitfalls in diagnosis, there are difficulties in estimating accurately the severity of this disease, the progress of the condition, and the results of therapy, all of which make objective evidence the more desirable.

In an attempt to supply this need we have been studying the effect of measured amounts of exercise on the symptoms and electrocardiograms of a number of patients. In some of the subjects the diagnosis was previously uncertain, in others a diagnosis of angina pectoris had been made unequivocally. Before describing our method and results, it will be profitable to examine the work already done in this field.

Transient changes in the electrocardiogram have been described by various investigators³⁻²⁰ during spontaneous as well as induced attacks of angina pectoris. Most of the described changes have concerned the direction of the T-waves, and the relationship of the RT or ST interval to the iso-electric line. Other subjects have shown, either alone or in conjunction with the above changes, transient bundle branch block (Bousfield⁷), transient auricular fibrillation (Parkinson and Bedford⁸, Arrilaga¹²), premature contractions (Hall⁸), lowering of the QRS voltages, and inversion of the T-waves (Vela¹³).

* Received for publication September 20, 1937.

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[†] We have considered angina pectoris to be a symptom due to deficient circulation of the myocardium, rather than a disease entity in itself.

Siegel and Feil¹⁶ have shown that such changes in the electrocardiograms do not accompany pain arising from other causes such as uterine contractions in labor or from gall-bladder or renal colic. In one patient with a gastric ulcer and paroxysmal epigastric pain, slight depression of the T-wave occurred, which varied in successive beats and was perhaps related to changes in the axis of the heart.

Whitten and Herndon¹⁴ have carefully analyzed a series of 50 normal controls, 15 cases of angina pectoris, and a small series of patients with heart disease other than angina pectoris. This work included a study of electrocardiograms (conventional three leads) taken at rest and immediately after exercise. Eight (53 per cent) of their 15 angina pectoris patients showed some of the following changes in the electrocardiograms which were not seen in the two control groups:

- “(a) Upright T_1 and T_2 became inverted,
- (b) Inverted T_2 became upright (Also in angina group that did not develop pain on test exertion),
- (c) Iso-electric T became upright (Also in angina group that did not develop pain on exertion),
- (d) Upright T_2 became diphasic,
- (e) Development of upward convexity of the RS-T interval ending in an inverted T (Coronary T-wave),
- (f) Increase in the “positivity” of the RS-T. of more than 0.1 mm produced by exercise in an already elevated RS-T,
- (g) The only Q greater than 1.0 mm in amplitude that disappeared on exercise was in the angina group.”

Many who have worked in this field have commented that in some of the normal subjects after such strenuous exertion as marathon running, there may occur a depression of RT_1 and RT_2 , or RT_2 and RT_3 to as much as 1.0 mm below the iso-electric line. This finding frequently occurs during attacks of angina pectoris. However, there is a tremendous discrepancy between the amounts of work required to produce such changes in these two groups of subjects, and furthermore, the underlying mechanism is probably the same, namely myocardial anoxemia.

Wood and Wolferth⁷ described transient changes after exercise in the RT intervals and T-waves of 15 (50 per cent) of the 30 cases of angina pectoris. Goldhammer and Scherf¹⁷ reported similar changes in 30 (75 per cent) of 40 patients with angina pectoris, and Duchosal and Henny⁸ found the test positive in 11 (58 per cent) of 19 true cases, doubtful in one, and negative in seven cases of angina pectoris. These last workers observed the test to be positive in seven of 24 doubtful cases of angina pectoris, doubtful in four, and negative in 13 cases.

It will be observed that a considerable percentage of seemingly typical cases in each of the above series showed negative electrocardiographic (3 lead) tests after exercise. Possible explanations are (1) insufficient exer-

cise in those who did not develop pain, (2) mechanisms other than anoxemia being factors, or (3) the possibility that the process was in so-called "silent areas" not reflected in the conventional three leads. It occurred to us that additional information might be obtained from a study of the effect of exercise on the chest leads as well as on the conventional three leads.

So far as we have been able to learn from a survey of the literature, Katz and Landt¹⁸ are the only workers who have studied the effect of exercise on the chest leads as well as the conventional three leads. Personal communications^{21, 22} from some of the workers in this field indicate that no work has yet been published on the effect of exercise on the chest leads of normal subjects. The series of Katz and Landt consisted of 20 ambulatory angina pectoris patients. They found transient changes in the chest leads in 11 of the 20 patients, in two of this group the changes occurred in the chest lead alone, in the other nine patients changes occurred in all four leads. That the amount of exercise (dumb-bell swinging while recumbent) may have been insufficient is suggested by the fact that pain occurred in only 13 of the 20 subjects. After reviewing their tables, we remain of the opinion that some of the changes they have described are not typical of angina pectoris. According to our own experience certain of these changes may occur in the electrocardiograms of normal subjects after exercise. We refer especially to the deepening of the normally inverted T-wave in the chest lead. Likewise, a slight depression of the RT interval may occur in any lead of some few of the normal subjects, even to 1.0 mm ($\frac{1}{10}$ millivolt) below the iso-electric line.

We have been able to confirm the experience of most of the other workers³⁻²⁰ in this field concerning the significance of transient inversion of an upright T₁ and T₂, or an upright T₂ and T₃, and/or significant changes occurring in the ST segments, after exercise, in the electrocardiograms of subjects with known or suspected angina pectoris. We are convinced that these changes do not occur in normal subjects and that these findings must be considered positive evidence of myocardial ischemia. Moreover, our studies of the chest leads of angina pectoris patients after exercise have led us to believe that *the same significance must be given to a shift of the RT segment in the negative direction or the temporary disappearance of the Q-wave in this lead, or a change from a normally positive T-wave to a negative one.* These changes have never been seen in our normal subjects. In the series of Katz and Landt¹⁸ the upward (negative) shift of the RT in the chest lead occurred four times in 20 tests, three times with changes in the conventional lead and once alone. Whitten and Heindon¹⁴ found one patient among 15 with angina pectoris in whom a Q-wave in the conventional leads greater than 1.0 mm in amplitude disappeared after exercise.

We are collaborating with Drs. Grant Otis and Joseph K. Bradford in a study of the effect of exercise on the chest lead as well as on the conventional leads of a group of normal subjects. This work will form the basis of another publication.

So far we have studied the effect of exercise on the conventional as well as Lead V of a group of 40 normal individuals varying in ages from 20 to 55. After such exertion as rapidly ascending from three to six flights of stairs, we have noted in addition to the temporary increase in rate the following transient changes in the electrocardiograms. In some, the T-waves increased in voltage, in others, they decreased. A few showed changes in the RT intervals in the negative direction to 1.0 mm below the iso-electric line. A few showed slight changes in the electrical axis. In none of these subjects was the direction of the T-wave changed, nor did we find any of the changes in the chest lead described in our angina pectoris patients during induced attacks of pain.

METHOD OF STUDY

Any method used for the study of pain and other symptoms in patients with coronary disease or allied conditions of myocardial ischemia should be reasonably accurate and as nearly free as possible from untoward effects.

Such a method of study we believe available in the use of the so-called "Standard Two-Step," utilized originally by Master and Oppenheimer²³ in a study of the response of pulse and blood pressure to a standard amount of exercise. It was used later by Riseman and Stern²⁴ in their studies on the amount of work required to produce attacks of angina pectoris.

The apparatus used is a two-step staircase. This apparatus has many advantages. The exercise of walking up and down steps is a familiar one and requires only brief directions. The amount of exercise can be readily varied and regulated. If the patient should develop any symptoms, the activity can be immediately stopped and the patient rested and studied in the very room in which the exercise is performed. Its comparative mobility, low cost, and ease of storage are additional advantages for the physician in private practice. The number of foot pounds of work performed may be estimated roughly by multiplying the patient's weight by the height of the staircase (1½ feet) and the number of trips performed (a trip consisting of a single ascent and a descent). This is inexact, however, for it ignores the work done in descent of the stairs. We have been able to confirm by repeated tests the relative constancy of effort required to produce the earliest symptom of discomfort in the individual exercised. Patients were never told their exercise tolerance. In this way the element of suggestion was lessened.

In our opinion the temperature of the ordinary office does not vary sufficiently to affect materially the amount of work necessary to produce discomfort. Wayne and Graybiel²⁵ also indicate that the temperature of the environment is not a very important factor. Riseman and Stern, however, have shown that in some patients a low environmental temperature is prone to precipitate pain with less effort. This particular point deserves further study in view of recent work indicating the effect of cold on the blood pressure.²⁶

Riseman and Stern used as their "end point" the amount of exercise producing sufficient pain to stop the patient. Because of our inexperience with the method and fear of possible danger to the patient, we have taken as our "end point" (after our first few tests) the earliest discomfort indicated spontaneously by the patient.*

*The exact nature of pain production in the heart is not clear. From the work of Lewis, Piekering, and Rothshild²⁸ one learns that the pain following the contraction of skeletal muscle during ischemia (tourniquet) is associated with actual dilation of blood vessels.

The bulk of experimental work favors the view that pain is due to chemical irritants arising from reduction or cessation of blood supply. Briefly summarized, the evidence for the so-called "ischemia theory" follows:

(1) Ligation of a coronary artery branch results in changes of electrical potential in the area affected and produces characteristic changes in the electrocardiogram.^{29, 30} When the arteries studied are only clamped, these changes are temporary and are quickly reversed upon restoring continuity of the artery.^{31, 7} The changes referred to are greater inversion of previously negative T-waves in some experiments and the production of a high take-off in the ST complex in others. In unanesthetized animals objective evidence of pain occurs.^{32, 33}

(2) Similar electrocardiographic changes occur during attacks of angina pectoris and disappear between attacks.^{3, 20}

Three possibilities present themselves:

- (1) That lack of oxygen is itself the stimulus,
- (2) That some condition resulting from anoxemia is the stimulus,
- (3) That irritable substances resulting from the metabolism of muscle, which are not washed away for lack of blood, constitute the stimulus.

The theory that pain is related in some way to anoxemia is supported by the following:

(1) Attacks of pain occur in conditions in which the oxygen content of the blood is low as in anemia⁴⁴ or in carbon monoxide poisoning.³⁵

(2) Angina pectoris frequently occurs in the presence of aortic insufficiency (low diastolic pressure) or in patients known to have had coronary thrombosis.

(3) Attacks of pain can be induced in susceptible subjects by rebreathing low oxygen mixtures or by strenuous exercise which creates a state of anoxemia generally referred to as "oxygen debt."^{19, 36, 37, 38} Such attacks have been found to produce characteristic electrocardiographic changes resembling those following coronary occlusion. Katz,³² however, has demonstrated that the electrocardiographic changes and production of pain do not necessarily go together. For in many instances exercise or relatively low oxygen mixtures caused the electrocardiographic changes without pain in normal subjects or even in patients with a history of anginal attacks.

Lewis^{39, 28} concluded after studying the development of pain in contracting skeletal muscles:

- (1) That special metabolic products (*P*-factor) formed by contracting but not by resting muscles stimulate pain endings,
- (2) That the locus of their action is in connective tissue and not within muscle cells, and
- (3) That the chief value of a good circulation resides in its ability to flush these substances away and not in its ability to supply oxygen. However, Kissin³⁸ offers evidence that oxygen lack may be an important factor in the production of pain. He observes that anoxemia produced by breathing low oxygen mixtures reduced the time necessary to produce pain in an exercising limb but the degree of anoxemia had to be rather severe in order to become a factor in the production of pain in an exercising muscle.

Katz³² concludes: "It would appear that the stimulus for pain is a metabolic product (or products) which can readily diffuse into the blood stream and which can be quickly altered in the presence of an adequate supply of oxygen. The accumulation of this product is dependent upon the amount and character of the physiological work and the efficiency on the one hand, and the quantity of oxygen and blood supply on the other. When this substance reaches a concentration above the threshold of the pain end organs, pain results. The chemical product appears to be acid in character, or at least one that is additive with acid substances and is 'neutralized' by alkaline substances. In all probability it is some substance like lactic acid or phosphoric acid formed during the catabolism of muscular activity."

Riseman and Stern studied over 500 induced attacks in 57 patients diagnosed as suffering from angina pectoris. No untoward effects were discovered from the exercise or the induced attacks. Other factors affecting the amount of exercise required to produce pain in a given individual were found to be excitement, recent ingestion of food, previous medication (nitrates), recent attacks of pain, and recent exertion. Thus far we have studied 94 attacks in 40 patients by this method. None has experienced any inconvenience or ill effect, and all have expressed willingness to repeat the test. In every instance the symptoms lasted less than four minutes and disappeared spontaneously.

In addition to determining the amount of exercise necessary to produce discomfort in these patients, we have also observed the effect of the exercise and resulting pain on the electrocardiogram, conventional three leads as well as chest lead. The position of electrode on the chest was marked and the identical area used in the subsequent tests*. In all instances an electrocardiogram was taken after a rest period of 30 to 60 minutes. The importance of this rest period is pointed out by Duchosal and Henny⁶ who made the following interesting observation. An electrocardiogram was taken of a patient after a night's rest in bed. During the next hour and 25 minutes, the patient was permitted to walk around his bed a few times, following which he rested 35 minutes. Another electrocardiogram was then taken. No pain occurred during the two hour interval, yet the second electrocardiogram showed a distinct drop of the T-wave and a slight drop of ST when compared with the earlier (basal) electrocardiogram. We feel that it is desirable to use the same basal conditions as for metabolic determinations.

The speed of the string type electrocardiograph made it preferable for our studies. Not infrequently, we have been able to take a four lead electrocardiogram (standard leads and one chest lead) in 75 seconds (10 to 12 cycles per lead) whereas trials with two of the older amplifier type machines required from six to ten minutes for similar determinations. Both timings were made with the electrodes attached to the subject and, in the case of the amplifier type machine, after the current had been turned on for a sufficient period. The time loss is due to oscillations of the light beam as connections are made for the various leads. In some of the newer amplifier machines, this difficulty seems partially corrected. Ease of standardization is an advantage of the amplifier type apparatus.

The necessity for speed arises from the importance (emphasized by Scherf²⁷) of comparing with the resting electrocardiogram the tracings taken immediately after exercise and at stated intervals following. The advantage of speed of operation is well illustrated in the electrocardiograms of our first patient (Figures 1 *A* and *B*). Significant changes were seen

* The right arm electrode was held at the left fourth intercostal space near the sternal border and the left leg electrode used as the indifferent electrode.

in the tracing taken immediately after exercise. The tracing taken five minutes after exercise disclosed only insignificant changes with reference to the resting electrocardiogram, considering that inversion of T_c may occur in normal subjects after exercise.

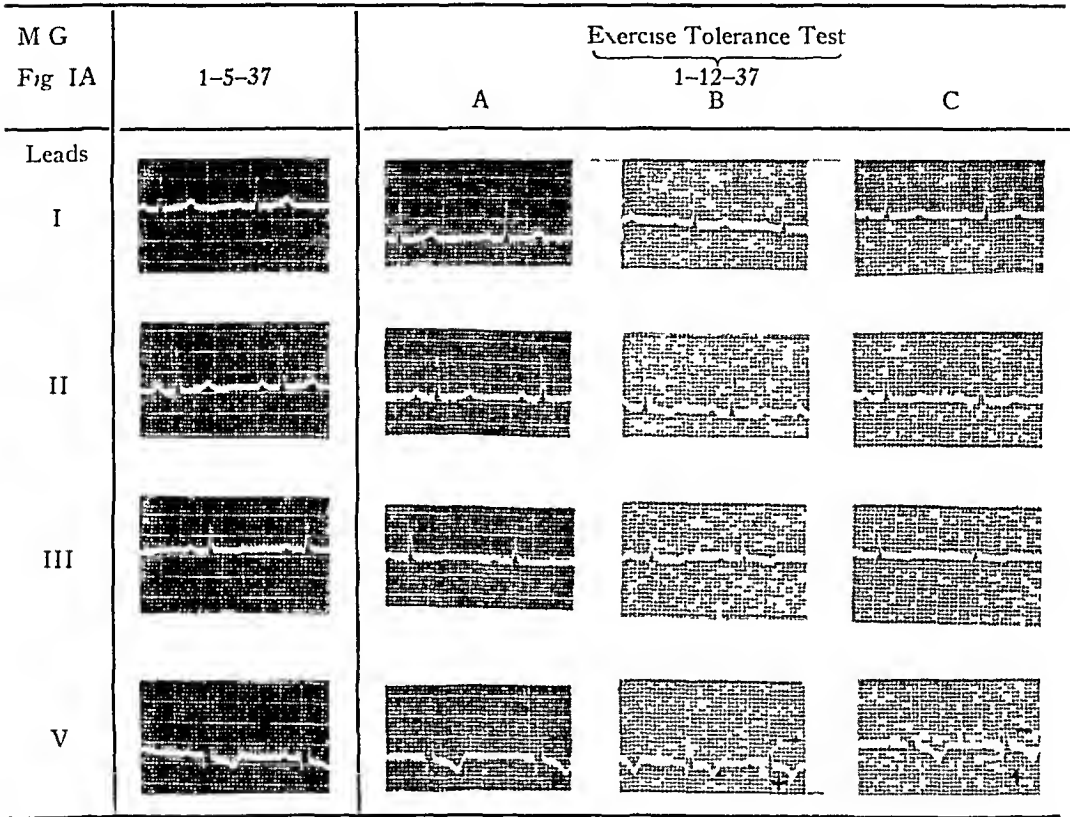


FIG 1-A January 5, 1937 Routine electrocardiogram shows no preponderance of either ventricle, normal T-waves, and normal RT intervals. Rate is 60. PR measures 0.20 second. Normal chest lead.

January 12, 1937 Exercise tolerance test shows

- A Resting electrocardiogram is identical with the tracing taken on January 5, 1937. Rate is 60.
- B Electrocardiogram taken immediately after exercise, consisting of 27 trips on the standard steps in 2½ minutes. Rate is 68. Note changes in T_1 and T_2 . T_2 has become diphasic and RT_2 has dropped below the iso-electric line. T_1 has become inverted. T_c has dropped to 10 mm. The chest lead shows very little change from the chest lead of the resting electrocardiogram. The T-wave in this lead reaches but 2.5 mm below the isoelectric line as compared with 4.0 mm in the resting tracing.
- C Electrocardiogram taken five minutes after the exercise was finished. Rate remains at 68. The tracing has almost returned to the resting appearance. Note the return of RT_c to the isoelectric line. T_1 is still lower than in A. The chest lead is identical with the one in A. The location of the chest electrode is the same for electrocardiograms A, B, and C.

Electrocardiograms of Patient M G. All electrocardiograms have been taken with the standardization of 1 cm equal to 1.0 millivolt. The connection for Lead V is made between the electrode placed at the left sternal border and the left leg.

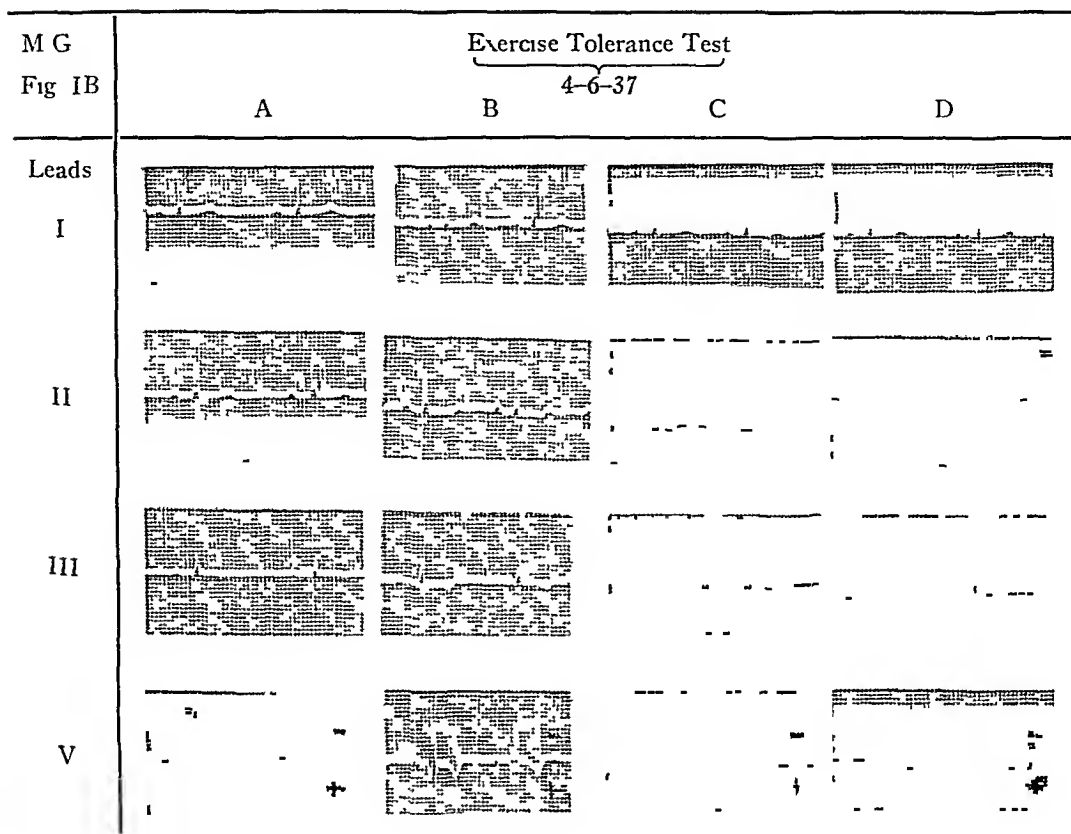


FIG 1-B April 6, 1937 Exercise tolerance test shows

- A* Resting electrocardiogram. Rate 54 Sinus bradycardia PR measures 0.22 second T_1 measures 12 mm T_2 measures 10 mm The chest lead is within normal limits
- B* Taken immediately after 23 trips on the standard steps No symptoms noted as a result of the exercise Rate rose to 66 T_1 remains unchanged T_2 is diphasic and associated with a lowering of RT T_3 is sharply inverted The chest lead is unchanged
- C* Electrocardiogram taken three minutes after the exercise No change in rate More marked changes in T and T_1 T_1 is also slightly lower
- D* Electrocardiogram taken 10 minutes after the cessation of exercise shows a return to the resting electrocardiogram (See electrocardiogram *A* above)

CLINICAL APPLICATION OF WORK TESTS

Case History 1—Showing marked electrocardiographic changes after slight exercise without production of pain Patient has coronary disease, a low basal metabolism, and a hyperchromic anemia

Miss M G, a 56 year old graduate nurse, presented herself for examination on March 18, 1937, because her "heart was not strong enough to carry on" Although she considered that the onset occurred suddenly in April 1935, during a period of great anxiety and overwork, closer questioning revealed that for 10 years she had had a "fatigue pain" under the left scapula This was definitely related to overexertion, it would occur at the height of activity, and disappear after one-half hour's rest

One night in April 1935, she noted an irregular beating of the heart and a "fear of sudden death" Pain suggesting the acute closure of a coronary artery was not noted Also about this time she was awakened by severe dyspnea This was immediately and completely relieved by standing Although she was able to assume her duties that day, her physician insisted upon her staying away from work for a period of time She remained at home for 11 weeks, but during this time the re-

sponsibilities of caring for an invalid father interfered with rest. About the same time there occurred a gradual change in the back discomfort. This "fatigue" pain now would radiate to the left breast and substernal region. Nitrites have never been used.

Of interest in the past history was an anemia discovered in 1928 (red cells, 2,800,000, hemoglobin, 50 per cent). Her basal metabolism was 4 plus. A gastrointestinal roentgen-ray series was negative. Cholecystograms were not made.

For the past two years she has had great difficulty keeping warm and would use hot water bottles in bed. At night twitching of the feet and thighs disturbed her.

Since 1934 she has taken thyroid extract gr $\frac{1}{2}$ (0.03) (Parke-Davis) daily and a preparation of liver extract. A blood count on 3-30-37 was reported: hemoglobin, 86 per cent, red cells, 3,999,000, and white cells, 5,400. Another on 1-30-38 showed hemoglobin, 73 per cent, R B C 3,900,000 and the smear showed macrocytosis, anisocytosis and a rare basophilic red cell. A gastric analysis has not been done because of the underlying cardiac condition. The patient has recently been started on dilute hydrochloric acid with meals and injections of a potent liver preparation.

Physical examination showed: Weight was 177½ pounds. Height was 59½ inches. There was a slight yellowish tint of the skin, but no signs of myxedema. The ocular fundi were negative. The peripheral arteries were soft. Blood pressure was 134/80. The heart was normal in size both on physical examination and by roentgen-ray. The lungs and abdomen were negative.

Her basal metabolic determinations are listed.

Date	Basal Rate	Remarks
4-9-37	-40%	Thyroid omitted for 10 days
4-23-37	—	Started thyroid (Armour's) gr 1 (60 mg) daily
5-7-37	-40%	Taking thyroid—same dose
6-4-37	-36%	Taking thyroid—same dose
7-10-37	-31%	Taking thyroid—same dose Feeling much better
9-2-37	—	Exercise test
9-4-37	-33%	Same dose thyroid
12-4-37	-31%	Improvement maintained Thyroid reduced to gr $\frac{1}{2}$ (30 mg)
1-28-38	-35%	Feeling about same On same dose thyroid
2-1-38	—	Exercise test

Other laboratory findings were: Blood calcium was 10.8 mg per cent, phosphorus, 3.1 mg per cent, cholesterol, 625 mg per cent and N P N, 37 mg per cent. Blood Wassermann and Kahn tests were negative.

Resting electrocardiograms taken at intervals since March 1935 had shown inconstantly a slight prolongation of auriculo-ventricular conduction to 0.22 second. Lead V was normal. Because her symptoms so overshadowed the objective findings, we obtained permission from Dr B. J. Slater to make exercise studies. In this we received the hearty cooperation of the patient.

Exercise Tolerance Tests

Date	No of Trips	Time	Remarks
1-12-37	27	2½ minutes	No pain felt. Admitted some dyspnea after questioning (figure 1 A).
4-6-37	23	2¼ minutes	No pain or dyspnea (figure 1 B). (Test taken to study the changes in the absence of pain.) (BMR—40 per cent.)
9-2-37	23	2¼ minutes	Patient asked to stop the test because of marked chest pain. Had taken desiccated thyroid for 2 months (BMR—31 per cent, —33 per cent).
2-1-38	25	2½ minutes	Slight shortness of breath. Patient asked to stop because of tightness in chest.
	29	2¼ minutes	No pain or objective dyspnea.

Although compatible with a diagnosis of coronary artery disease, this patient's history was remarkable for the meagerness of objective evidence implicating the circulatory system. It is probable that her anemia contributed greatly to her cardiac symptoms and that her marked symptomatic improvement during the past six months may be partially explained by the increased oxygen carrying capacity of the blood, consequent to the improvement of the anemia. The anemia itself may be partially the result of hypothyroidism. The cardiac symptoms in the presence of a low metabolic rate deserve comment in view of the recent vogue for completely removing non-toxic thyroid glands. These operations have been done on other patients in an attempt to establish clinical improvement by decreasing the demands on the circulatory system. Our patient's problem is further complicated by the possibility of inducing more cardiac symptoms if the metabolic rate is increased by the administration of thyroid substance. On the other hand, some of her cardiac symptoms may be the result of hypothyroidism. The transient changes in the T-waves and RT intervals of Leads II and III seemingly give objective evidence of impaired coronary circulation.

On June 4, 1937, her basal metabolic determination was minus 36 per cent after having taken desiccated thyroid 30 mg (gr $\frac{1}{2}$) daily for three weeks. Upon resuming this medication, she felt improved. The dose was then increased to 60 mg (gr I) daily with subjective improvement, although the patient was still having some cardiac symptoms particularly at night. On September 2, 1937 there was apparently a decrease in her exercise tolerance, in that after 23 trips she asked to stop by reason of pain. This is comparable with Blumgart's⁴² experience with patients who developed myxedema after total thyroidectomy for angina pectoris. Relatively small doses of desiccated thyroid substance were sufficient to diminish the gains in exercise tolerance made through the operation.

Case History 2—Illustrating the effect of exercise on the electrocardiograms of a patient with a duodenal ulcer and coronary artery disease complicated by a marked anxiety neurosis

The patient, Mr. A. T., a 43 year old clothing designer, was referred by Dr. Ellis B. Soble and Dr. George R. Lavine for cardiovascular study.

The important points obtained from Dr. Soble's record follow. Since 1932 the patient had complained of substernal and epigastric pain. History taking had always been affected by his extreme suggestibility and tendency to phobias. The onset of symptoms was sudden, immediately following the death of a friend from heart disease. The discomfort occurred after eating, was relieved by eructation, and was not affected by exercise. Relief was sometimes obtained by an enema. His general physical examination was negative, and the blood pressure varied from 140 systolic and 80 diastolic to 160 systolic and 100 diastolic. Gastrointestinal roentgenological studies showed evidence of duodenal ulceration. Marked relief was obtained by the administration of a bland diet and alkali, although, for a short while, he continued to have some of the discomfort in his chest. He was free from precordial discomfort until November 1935, when it recurred for a short time with numbness of the left arm. Throughout this period, the patient had been difficult because of hysterical symptoms. He remained relatively well until July 1936, when there occurred a sudden attack of severe epigastric pain. A diagnosis of perforated ulcer was made and

confirmed by operation. A resection was done, and convalescence was uneventful. In January 1937, his only complaint was "heart ache." The patient was uncertain whether or not he obtained relief by nitroglycerine. It was because of the persistence of these symptoms that he was referred to us for further study.

An insight into the psychiatric background was given by Dr. Lavine who summarized his studies as follows. The patient has always been shy, seclusive, and self-conscious. In his earlier years he had been protected by an older brother. After the brother's death, he became fearful and developed "shaking spells." He was irritable, apprehensive, and had definite sexual disabilities. He also had a fear of developing insanity. Since the sudden death of his friend, the patient thought that he had heart disease.

We first saw him in May 1937, and at that time he described the occurrence one week before of a pain in his left shoulder, numbness of the left arm, a "heaviness" over the upper sternum, and a tightness in his throat. Partial relief was obtained by resting, but greater relief was experienced after drinking a glass of water. It was hard to get a clear appraisal of his symptoms because of his proneness to contradict himself.

Since his operation eight months before, he had been conscious of hyperesthesia of the left shoulder region. In the morning when stooping to pick up his shoes, he would note a "cramp" in his left shoulder. The symptom, however, might occur at any time by "thinking about it." It was also noted in the morning when walking 15 yards to his garage. Bending to enter the car would increase the pain near the distal end of his left clavicle. It would radiate to the suprasternal notch and interscapular region and would last for 15 minutes. It was unaffected by breathing and was partially relieved by eructation or taking soda bicarbonate. The patient was not certain that nitroglycerine gave any relief, nor was he certain that he could produce the symptom by walking any other time of the day. He had been able to continue his daily work and apparently had very little difficulty except for the short period after breakfast.

His physical examination was essentially negative. The blood pressure was 146 systolic and 80 diastolic. The carotid sinus reflex was very active. Fluoroscopic examination of the chest was negative.

A single resting electrocardiogram, taken on May 8, 1937, showed very little change from the normal. The patient had experienced a severe pain two hours before the tracing was taken. T_1 was slightly diphasic, but it would be difficult to rule out the presence of a U-wave. The slight depression of RT_2 would not be given much significance by most clinicians. The presence of the diphasic T-wave in the chest lead is a possible deviation from the accepted normal.

Edekin, Wolferth and Wood⁴⁰ offer evidence that a diphasic T-wave in the chest lead or an upright T-wave in this lead are suggestive of heart disease. However, because many patients showing such borderline changes in their electrocardiograms are free from symptoms of cardiac disease and because of the extraordinary combination of gastrointestinal, cardiovascular, and mental symptoms in one patient, we felt it important to obtain as much objective evidence as possible.

It was with this in mind that we determined to study the effect of exercise. On June 5, 1937, two hours after a very light lunch and one and three-quarter hours after resting in recumbency, his basal electrocardiogram (A) was taken following which he was exercised at the rate of 12 excursions per minute.

Elapsed time in minutes	No of trips	Remarks
0	27	"A little pain"
	34	(Pointing to left shoulder) "not bad"
	43	"Getting worse"
3 45	44	Exercise stopped

The electrocardiograms taken before exercise (figure 2) on June 5, 1937, showed no deviation from the normal in the standard three leads. However, T_6 was diphasic. Electrocardiogram B started 75 seconds after the cessation of exercise, showed a drop in voltage of T_1 , a depression of RT_2 and RT_3 , and a change of T_2 and T_3 from positive to diphasic waves. The

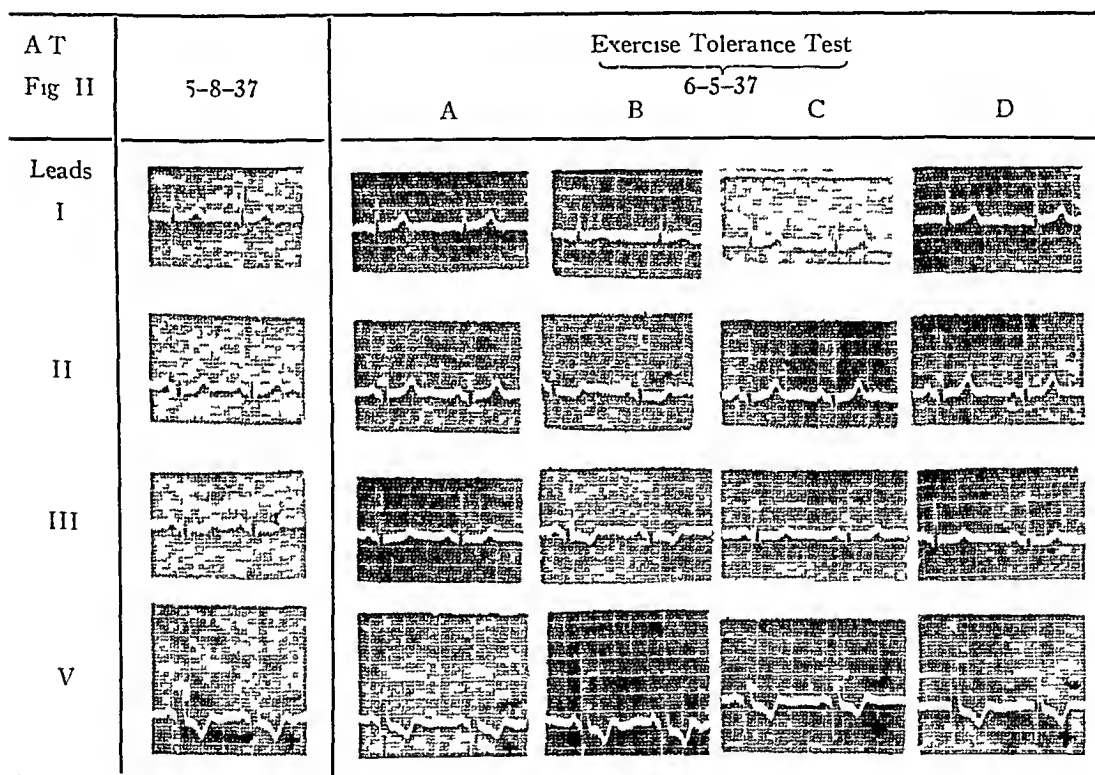


FIG 2 Electrocardiogram of Patient A T

May 8, 1937 Rate, 72 Slight depression of RT . T_1 is slightly diphasic. Patient had severe spontaneous attack of pain two hours before this electrocardiogram was taken. The chest lead shows a diphasic T-wave.

June 5 1937 Exercise tolerance test shows

A Resting electrocardiogram shows normal three conventional leads and diphasic T_3 . Rate is 65.

B Electrocardiogram taken 75 seconds after exercise. Rate is 60. T_1 has dropped and is slightly diphasic. T_2 and T_3 have become diphasic and are associated with a drop of the RT interval. The chest lead remains unchanged.

C Electrocardiogram taken 10 minutes and 15 seconds after exercise. The tracing has almost returned to A above. Rate is 58. T_1 is still slightly lower than T_1 in A.

D Electrocardiogram taken 16 minutes after exercise shows no change from A.

chest lead showed no significant change from the resting one. In electrocardiogram C, started 10 minutes and 15 seconds after the cessation of exercise, one notes almost a return to the resting electrocardiogram. T_1 is still a little lower than in electrocardiogram A. Electrocardiogram D, taken 16 minutes and 15 seconds after the cessation of exercise, duplicates the resting electrocardiogram.

The transient changes in the standard leads taken immediately after exercise would seem to give objective evidence of "myocardial ischemia."

Case History 3—Showing the effect of exercise on the electrocardiogram of a diabetic with symptoms of coronary disease. A routine electrocardiogram was essentially negative, the exercise test showed changes most marked in the chest lead.

Mr. E. C., a 46 year old tailor, was first seen on August 15, 1936, because of "back pain" and a "tight feeling" in his chest if he walked one block. His symptoms started gradually three years before. However, following the discovery of diabetes mellitus in 1934 and its control by diet, he felt well until four months before his first visit to our office. At that time, while ascending a flight of stairs, he experienced a sudden pain in his left scapula. Because this persisted for 24 hours he visited a physician, who bled and massaged his back. The pain was also noted over the front of his chest, more on the left than right side. He continued to work, although throughout that week he had the same discomfort every morning after ascending one flight of stairs, or if he walked more than one block. The discomfort would start in both scapulae, radiate over the top of the two shoulders to the left breast, and then to the right breast. At such times he became dyspneic and had to stop. His diabetes has remained under control by dietary means alone.

Physical examination showed his weight to be 171 pounds. Height was 5' 2½". Blood pressure was 132/80. The peripheral and retinal vessels were normal. Heart sounds were distant and the rate was 80. The heart was otherwise negative. Rhythm was regular. Moderate emphysema of the lungs was present. The abdomen was negative.

Laboratory tests showed the following: Blood sugar (mid-afternoon) three hours after a meal was 112 mg per cent. Blood Wassermann and Kahn tests were negative. Hemoglobin was 97 per cent. Red blood count was 5,500,000. White count was 5,800.

His exercise tolerance tests indicating the number of trips required to produce pain are shown in the table on page 2031.

It has been the experience of others (Riseman and Stern) that within limits the exercise tolerance is quite constant, and this was confirmed by our experience with a smaller series. Also, Brown and Riseman¹¹ have shown that an increase in exercise tolerance of 50 per cent or more usually caused a striking diminution or complete absence of attacks in daily life. Our protocol confirms the increase in exercise tolerance commented upon by Riseman and Brown in one of their recent papers¹² in which they described the beneficial effects of nitroglycerine and also xanthine derivatives on many of their angina pectoris patients. We heartily agree with their statement, "If medication induces improvement in a patient who has attacks on exertion, this improvement should be evidenced by an ability to perform more work than was possible without medication." In the protocol above on 11-20-37, it seems quite conclusively shown that for all practical purposes the effect of

Exercise Tests

Date	Remarks	No. of Trips† to Produce Pain
9-11-36	Phyllicin* started	19
9-28-36	Subjective improvement noted Placebo substituted (Soda mint)	34
10-31-36	Not feeling as well as with Phyllicin Placebo stopped Theocalcin† started	28
12- 5-36	Feeling about same Theocalcin stopped Nitroglycerine started thrice daily before meals and p r n	27
8-21-37	Subjectively much better Last dose of nitroglycerine 4 hours before test Using only one dose in a m and free from discomfort rest of day Walks home 5 blocks	27
9-10-37	Much subjective improvement since last visit Same regime	30
11-20-37	Feeling about same Last dose nitroglycerine 1 hour before test Pain lasted 3 minutes	32
	Allowed to rest 20 minutes and given nitroglycerine Test started 3 minutes later	70
	Patient stopped exercise chiefly because of leg pains Had only slight precordial pain	
1- 8-38	Not doing as well Glycosuria present Phyllicin started again	24
1-29-37	Clinically much improved Able to walk 7 or 8 blocks without pain	
	Pain started at	30
	Pain moderately severe at	36
	Electrocardiogram taken	

* Theophyllin—Calcium Salicylate

† Theobromine—Calcium Salicylate

‡ Rate 12 to 14 trips per minute

nitroglycerine had ceased before the first exercise test was performed, and that following its administration the exercise tolerance increased by almost 120 per cent

The changes in the electrocardiograms (see figures 3 A and B) are reflected chiefly in the chest Lead (V) We have not encountered in any of our normal controls after exercise the change from the normally inverted T-wave in the chest lead to one that is diphasic, preponderantly positive, and associated with an elevation of the RT interval above the iso-electric line as demonstrated in this patient

On the basis of this patient's symptoms and the transient changes in his chest lead after exercise, we made a diagnosis of coronary disease We suggest that such changes in the chest lead after exercise may be considered evidence of myocardial ischemia, even though the conventional three leads remain normal

DISCUSSION AND CONCLUSIONS

The earliest use of the electrocardiograph was directed to the analysis of abnormalities of rhythm and rate As experience was gained it was found that valuable information about myocardial function was obtainable from a study of the shape, amplitude and time relations of the individual deflections In more recent years the use of chest leads has frequently supplied information not obtained from the conventional three leads However in many

patients with definite impairment of myocardial circulation, all routine clinical tests may yield negative results

Methods are discussed for obtaining objective evidence of myocardial ischemia (angina pectoris)—where the diagnosis would otherwise rest solely upon a more or less ambiguous history—by comparing electrocardiographic tracings, after rest, immediately after a measured amount of exercise, and at successive intervals after the exercise, using chest leads as well as the conventional three leads. We have been able to confirm the significance of the transient changes in the T-waves and RT segments described by other workers³⁻⁵. Particular importance is attached to including

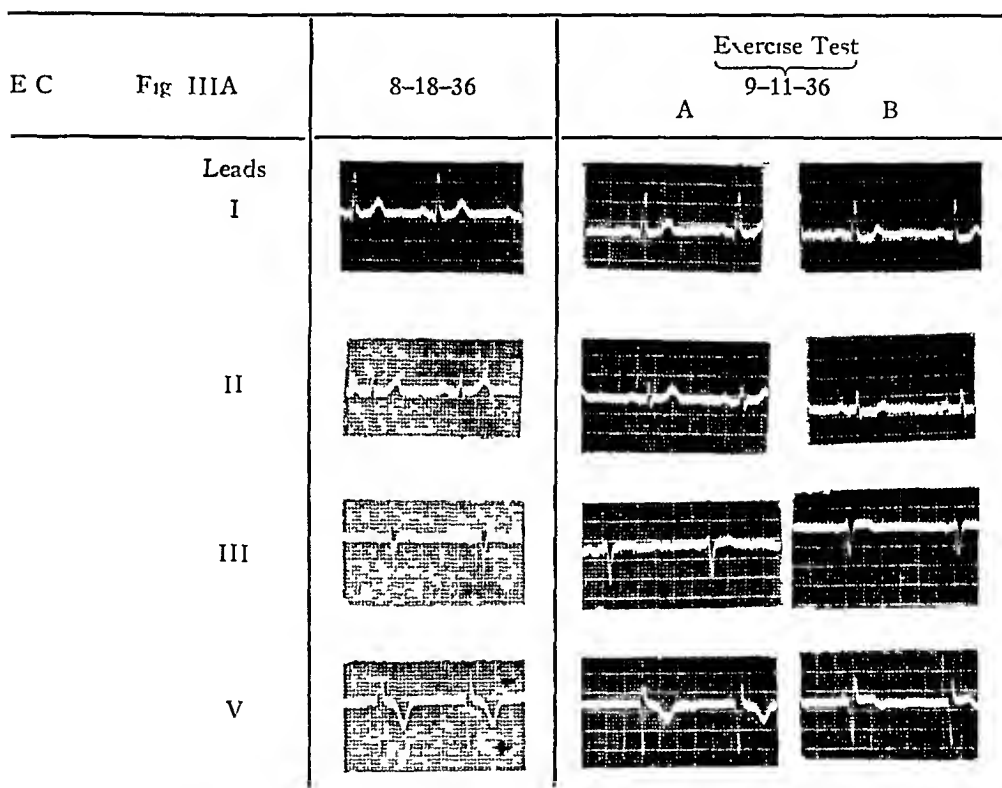


FIG 3-A Electrocardiogram of Patient E C

August 18, 1936 Resting electrocardiogram Rate 58 Normal T-waves and RT intervals Slurring and notching of QRS in all leads Left axis deviation Deep Q.

September 11 1936 Exercise test shows

A Resting electrocardiogram which is almost identical with the one taken on August 18, 1936 T_s reaches but 3.5 mm below the iso-electric line in contrast with 6.5 mm below the iso-electric line in the tracing of August 18, 1936 This difference in the T-wave may be the result of a change in position of the chest electrode The rate is 53

B Electrocardiogram taken immediately after 19 trips on the standard steps Rate 50 RT_1 and RT_2 are slightly lower and T_1 and T_2 have dropped slightly in voltage In Lead V there is seen a distinct change in direction of the T-wave which is now upright and associated with a high take off of the RT interval The chest electrode was placed in the identical area as in electrocardiogram A

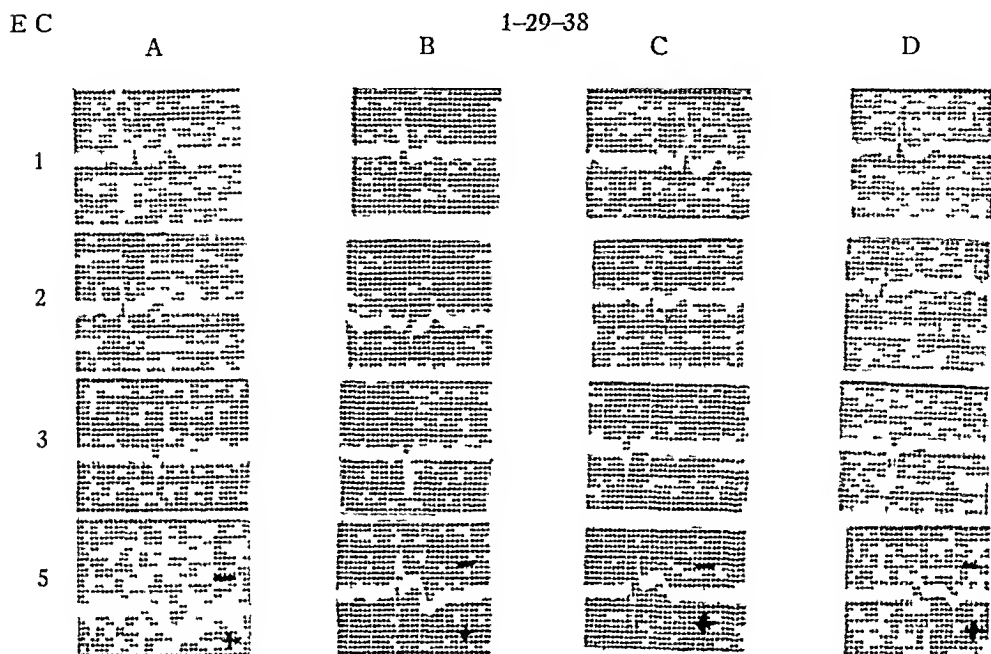


FIG 3-B Electrocardiograms of Patient E C, January 29, 1938

- A* Resting electrocardiogram Nitroglycerin $6\frac{1}{2}$ hours before No significant change from resting electrocardiograms on August 16, 1936 and September 11, 1936 Rate, 52
- B* Electrocardiogram after 36 trips Finished two minutes after cessation of exercise Rate 85-62 Observe negative shift of RT-1 and 2 and upward (negative) shift of the RT interval in the chest lead with a change in direction of T
- C* Started two and one-half minutes after *B* and finished in 85 seconds Rate, 65 Changes still persist in Leads I and II and are slightly less distinct in the chest lead
- D* Started two minutes after *C* (seven minutes after exercise ceased) and completed 75 seconds later Rate, 62 Shows less marked changes in Leads I, II, and V

the chest leads, since they sometimes yield positive information after exercise when the conventional three leads are negative. We have not encountered in any of our normal controls after exercise the change from the normally inverted T-wave in the chest lead to a diphasic or upright one with elevation of the RT interval nor have we noted the disappearance of the Q-wave in the chest lead after exercise. We believe that these changes may be considered objective evidence of myocardial ischemia. Electrocardiographic changes may occur after exercise even in the absence of pain production. (See Case History 1)

It is *not* to be assumed that negative results after the application of these tests disprove the existence of angina pectoris in the face of a history indicating its possible presence. At the present time it cannot be said that the tests have negative significance.

The tests are deprived of value unless the basal electrocardiogram is taken after adequate rest. Otherwise the contrast between rest and exercise is upset and the exercise administered is cumulative and incapable of

being accurately measured. At best there is only an approach to precision. For that matter, adequate rest is equally important before taking a routine electrocardiogram. The mechanism of individual cardiac attacks deserves study by this method also because in certain subjects these attacks may be the result of arrhythmias which, if recognized, may respond to appropriate therapy.

The history of the patient often indicates the approximate amount of exercise that can be tolerated. The work performed was measured on the "Standard Two-Steps," a method sufficiently simple and accurate to lend itself to clinical application. Such determinations may, of course, be made without observing the effect on the electrocardiogram. The methods used afford a possible means of observing the effect of therapy or the course of the morbid condition itself, inasmuch as a series of tracings, before and after exercise, may show changes where a series of tracings taken at rest do not.

In interpreting the tracings, it must be borne in mind that the mere fact that some changes appear does not necessarily indicate abnormality, since certain changes occur in normal subjects.

The coincidence of transient changes in the electrocardiogram with symptoms may in the selected atypical case establish a diagnosis otherwise uncertain (see Case History 2).

This method has proved entirely safe when the patient was admonished to stop on feeling any appreciable discomfort. Furthermore, in the hands of others, even when the exercise is carried to the point of causing pain severe enough to stop further activity, there have been no untoward results.

We wish to express our sincere thanks to Mr. Arthur E. Rosenberg for his assistance.

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CASE REPORTS

A CASE OF CHRONIC HEMORRHAGIC BRIGHT'S DISEASE ASSOCIATED WITH AN ANOMALOUS BASOPHILIC PITUITARY GLAND*

By RAYMOND F. HOLDEN, JR., *New York, N. Y.*

IT is the purpose of this report to present a case of chronic hemorrhagic Bright's disease in which a remarkable pituitary basophilism apparently contributed to the clinical picture.

F. B., an unmarried Jewess of 30 years, referred by Drs. J. Eidelsberg and J. W. Wilner of New York City, entered the Rockefeller Institute Hospital May 11, 1935, with complaints of swelling of the face and lower extremities, increasing weakness, and failing vision for one and one-half years, also obesity and diabetes for 10 years.

Family and Personal History. The patient was one of a family of four children, her three sisters were healthy. Her family history was notable in that both grandmothers had diabetes, her mother had suffered from nephrolithiasis for 13 years, while her father, a mild diabetic, was at the time confined to bed by a hemiplegia.

Her health, up until 10 years before admission, had been fair. She had measles, scarlet fever, and diphtheria during childhood without obvious sequelae. A marked myopia had been present since infancy. She had been classed as mentally retarded in school and did not finish the eighth grade. Her occupations had included millinery, clerical, and household work.

The onset of catamenia was at 13 years. Menstruation had been normal until the past two years when it had become scanty and irregular.

About 10 years ago she had suddenly grown excessively fat. Shortly after this, a diagnosis of diabetes had been made. She had followed dietary restrictions in desultory fashion and during recent months had taken from 10 to 20 units of insulin daily.

Present Illness. Edema appeared first in November 1933, following a cold. During the following six months she gained 20 pounds in weight. She entered the Post-Graduate Hospital in November 1934. A diagnosis of chronic nephritis was made and a high-protein, low-salt diet was prescribed. Her weight fell from 200 to 159 pounds during her three weeks' stay in the hospital. On discharge she was instructed to continue the diet and 20 units of insulin daily for the diabetes. Thyroid was administered for a short time, but it produced severe muscular cramps and had no effect on the edema. She neglected her diet and began to gain weight again, so that she weighed 198 pounds on admission to The Rockefeller Hospital.

Physical Examination. The patient was an obese young woman with generalized anasarca. Her face was so swollen that the palpebral fissures were closed, while her lower extremities exhibited massive edema. The skin of her neck hung in folds and the breasts were extraordinarily large and pendulous. Aside from the dependent edema her appearance was rather similar to the photograph of Case 2 in Cushing's series (Cushing (1932), p. 151). There was a myopia of 10 + D, which made examination of the fundi difficult. Retinal arteriosclerosis, scattered hemorrhages, and deposits of exudate were noted. There was a pronounced upper dorsal

* Received for publication May 24, 1937.

From the Hospital of The Rockefeller Institute for Medical Research, New York.

lyphosis. Moist rales were heard at both lung bases. The heart was not enlarged by percussion, but the aortic second sound was accentuated and the blood pressure was 224 mm Hg systolic and 116 diastolic. There were no signs of fluid in the large, flabby abdomen. The liver and spleen were not felt. Pelvic examination revealed a nulliparous cervix with a small amount of mucopurulent discharge, the fundus and ovaries could not be felt. The reflexes were sluggish.

Laboratory Data Roentgenograms of the heart and lungs demonstrated a relatively small thoracic cage, but no other abnormality. Lateral views of the skull showed a normal appearance of the sella turcica and cranial vault. Electrocardiograms indicated a normal cardiac mechanism with left axis deviation. The basal metabolic rate was plus 20 per cent, presumably due to thyroid taken before admission.

In addition to the data given in the graphic chart, the following laboratory findings were obtained: Blood non-protein nitrogen, 59 mg per cent, plasma free cholesterol 110 mg per cent, total cholesterol, 264 mg per cent, fasting blood sugar 65 mg per cent. After 100 gm glucose were taken by mouth the per cent blood sugar values were as follows: 1 hour, 112 mg, 2 hours, 138 mg, 3 hours, 99 mg.

Urine from the second half of a 24-hour Addis concentration test showed: Volume 950 cc, pH 7.0, specific gravity 1.0165 (corrected for protein), protein 7.9 grams per liter (7.5 grams per 12 hours), red blood cells 2.5 million in 12 hours, casts 140,000 (100 per cent hyaline), oval fat bodies. Subsequent laboratory findings are shown graphically in figure 1.

Clinical Course On the basis of the physical and laboratory findings, a diagnosis of chronic hemorrhagic Bright's disease was made. Single urine specimens showed persistent moderate glycosuria, not affected by administration of insulin, which was soon discontinued. Because of the peculiar obesity, high sugar tolerance, renal glycosuria, and menstrual irregularity a diagnosis of adiposogenital dystrophy was considered. The basal metabolic rate went to plus 43 per cent on a short course of thyroid, and the patient showed no improvement. She complained of constant pain in her thighs, also severe headaches. The blood pressure remained high and fresh retinal hemorrhages appeared. She lost weight (edema) rapidly on a high-protein diet with restricted salt, going from 90 kg on admission to 70 kg on discharge six weeks later.

After leaving the hospital she allowed her diet to lapse and began to grow edematous again. At the time of her second admission, three months later, she weighed 94 kg and appeared in every way the same as when she was first seen. The urea clearance was 12.5 per cent and the blood non-protein nitrogen 73 mg per cent. On the same diet given previously, her weight fell to 88 kg during three weeks in the hospital and she was again sent home. Edema returned promptly and she was readmitted a month later in an extremely weakened condition, despite efforts which had been made to provide a proper diet at home. The urea clearance was now 5.6 per cent and the blood non-protein nitrogen 102 mg per cent. At this time there were definite signs of fluid in her chest. She was again placed on a high-protein, low-salt diet and began to lose weight slowly. Increasing dyspnea and orthopnea set in and it was felt that cardiac decompensation had become a factor. Digitalis was given without any noteworthy effect. She complained of lower abdominal pain and had some vicarious menstruation. Nothing abnormal was noted on pelvic examination. During the following month signs of uremia supervened and she began to vomit with increasing frequency. The urea clearance fell to 2.5 per cent six weeks before death and remained at this level. She suffered a severe attack of secondary glaucoma and her vision failed completely, despite intensive treatment with eserine. Her weight dropped continuously, reaching 66 kg a week before death. The last complication to appear was a swelling of the right parotid gland, associated with cellulitis of the face and neck.

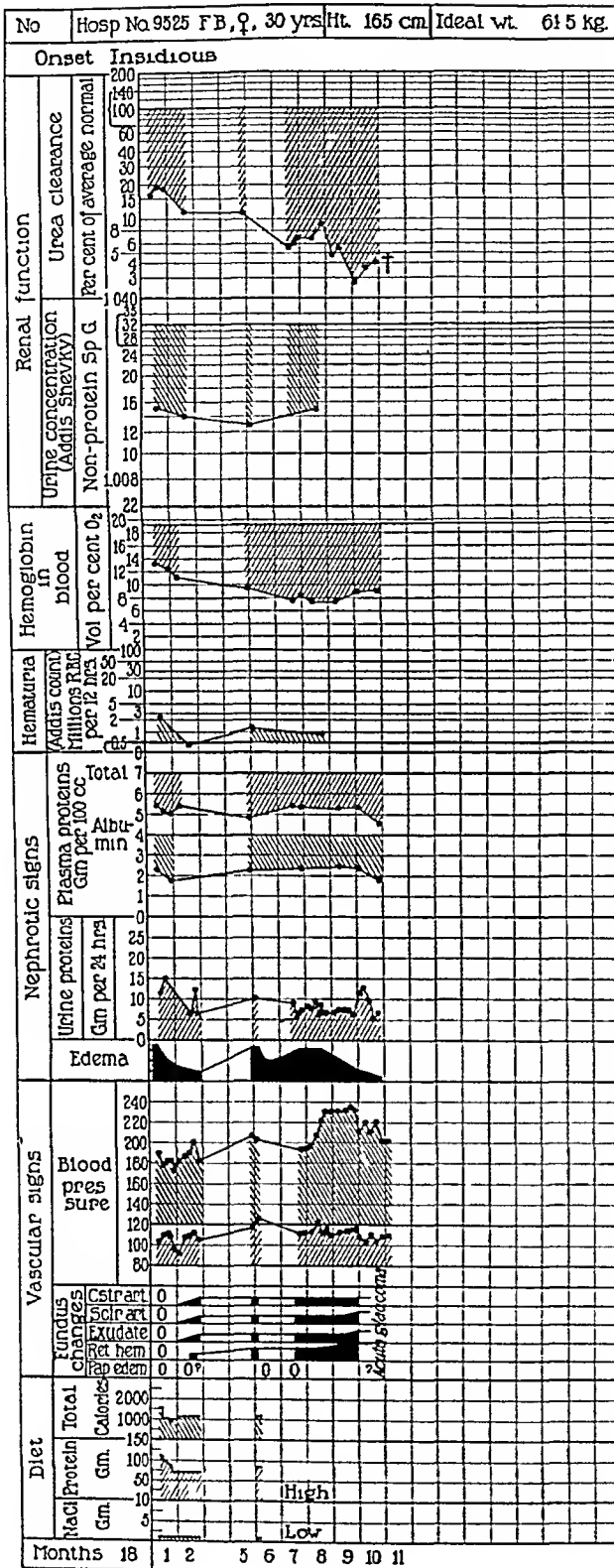


FIG 1 Chart of the laboratory findings in the patient

Autopsy The autopsy was carried out by Dr C P Rhoads, and the following data are from his record

A remarkable picture was presented by the pituitary gland and its environs (figures 2 and 3) The carotid bulbs extended to above the normal height and approached the midline to such an extent as to compress the hypophysis between them, so that its sides were concave and the antero-posterior diameter extended The vessels were soft and elastic, without aneurysmal change Microscopically, the anterior lobe was found to consist almost entirely of basophilic cells, with only a few groups of acidophilic cells The posterior lobe contained no adenoma and was not otherwise remarkable The kidneys were normal in size, shape, and consistency



FIG 2 Photograph showing a dorsal view of the pituitary in the sella turcica The carotid bulb can be seen on each side of the gland, somewhat separated from it for photographic purposes The lateral compression and deformity of the gland are well shown

The capsules stripped easily, leaving mottled brown-yellow surfaces which were slightly irregular The cortex was of normal thickness on section, but had a peculiar translucent appearance and presented scattered small yellow areas Many branches of the renal arteries were almost occluded by masses of atheromatous tissue The pelvis and ureters were not remarkable Microscopically, a very advanced chronic glomerulonephritis was apparent Hyaline deposits and endothelial proliferation within the glomeruli were present in various stages of development Fibrin thrombi were seen in some glomerular capillaries The tubules were dilated and showed widespread degeneration of the tubular epithelium The interstitial tissue was increased in amount and infiltrated with lymphocytes Intimal proliferation and atherosclerosis of the arteries were striking The left ventricle of the heart was

hypertrophied. Atheromatous areas were noted in most of the large arteries, especially in the renal arteries and their branches, the coronary arteries, and the circle of Willis. There were a few fibrous pleural adhesions and the lungs were moist, with frothy fluid in the bronchioles. The liver, spleen, and two accessory spleens appeared normal grossly. They showed some congestion on microscopic examination and there was much fat in the liver cells. The gastrointestinal tract, gall-bladder, and pancreas were normal. Both adrenals were grossly normal, while microscopically there was an excess of fat in the cortical cells. The uterus was small and the ovaries appeared normal, each containing corpora lutea. Multiple sections of the brain disclosed no abnormality.

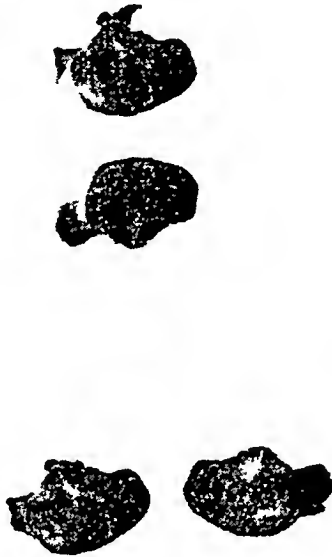


FIG. 3. Top photograph showing a lateral view of the pituitary after removal from the sella. The flattened lateral surfaces are well shown.

Bottom photograph shows the cut surface of the pituitary after sagittal section.

DISCUSSION

It seems reasonable to suppose that the anatomical defect of the hypophysis antedated the nephritis, since there was no evidence of recent change in the position of the internal carotid arteries. Search of the recent literature has not produced any mention of similar defects*. If this anomaly is a rare one, as seems probable, then its presence in a case of nephritis would appear to be merely a coincidence. From the standpoint of clinical diagnosis, the presence of a gross deformity of the pituitary gland which could not be detected by lateral

* In a personal communication to Dr Rhoads, Dr Cushing stated that he had never seen an anomaly of this type.

stereoscopic radiograms of the skull seems significant. While it is recognized that roentgen-ray diagnosis of a normal sella turcica does not necessarily exclude gross defects of the hypophysis, nevertheless the anomaly in this case occasioned considerable surprise at the autopsy table.

The basophilic hyperplasia found in the anterior lobe may have been a result of injury by the lateral compression. From their frequent occurrence in the clinical syndrome of pituitary basophilia, it appears that the obesity, glycosuria, and menstrual irregularity were resultant effects of the hyperplasia. The duration of these symptoms would suggest that the basophilic condition was present for some time before the onset of nephritis. The possible causal relationship between pituitary basophilism and renal disease has been discussed fully by Cushing (1932, 1934) and by MacMahon, Close, and Hass (1934). Cushing (1934) states that "It has been pointed out separately by Erdheim, Tolken, Kraus, and Berblinger that an increase of basophilic elements in the glands as a whole is an accompaniment of advancing years of life when naturally enough it is often associated with atherosclerosis and renal disease." Nevertheless there has been a high incidence of nephritis among the cases of basophile adenoma in young adults which have been reported since the clinical syndrome of pituitary basophilism was described by Cushing (1932). In Cushing's original series, five out of eight patients who came to autopsy presented chronic nephritis of some degree. The cases reported by MacMahon, Close, and Hass (1934), Russell, Evans, and Crooke (1935), and Close (1935) all exhibited renal damage in varying amount. Those of Pardee (1934) and Hildebrand (1935) were apparently normal in this respect, although Pardee made little mention of urinary findings. Cushing (1932) suggested that the nephritis in his cases was probably secondary to the hypertension. However, just as in malignant hypertension, there is no *a priori* reason to assume that the nephritis may not come to dominate the picture. In the present case, it is not known whether hypertension antedated the onset of nephritis. Since the pituitary symptoms were present at an earlier date and since the pituitary at autopsy showed no evidence of recent change, it may be supposed with some certainty that the basophilic hyperplasia was present before the nephritis.

The course of the patient's (clinical) condition, and of the renal, blood and circulatory pictures, were quite similar to those observed in typical progressive chronic nephritis, without the pituitary element. The onset was insidious and the disease progressed in a little over two years to a fatal outcome, in accordance with the clinical dictum that gradual onset lends a bad prognosis in hemorrhagic nephritis. Good nutrition was maintained on a high-protein, low-salt diet* until a few weeks before death. Despite the high protein intake, which included supplements of casein up to 30 grams daily, the plasma protein remained low, and the deficit was entirely in the albumin fraction. The excretion of urinary protein averaged about 10 grams daily. The effect of low salt intake showed itself promptly in loss of edema fluid on each admission. Anemia was rather marked, so that the hemoglobin values averaged about 50 per cent of normal during the last five months of illness. Hematuria was never excessive. The blood pressure and cardiac hypertrophy were not unusual for nephritis. Most

* An effort was made to keep the protein intake up to 100 grams daily during the first admission. Because of the patient's capricious appetite, this was not accomplished with any regularity. Salt intake was kept below 1 gram daily.

of the characteristics summarized by Page † (1936) for a typical case of progressive nephritis were present in this patient

SUMMARY

1 A case of chronic hemorrhagic Bright's disease with clinical features suggestive of pituitary dystrophy is described. The clinical impression of hypophyseal disorder was confirmed by the postmortem finding of a grossly abnormal pituitary gland which contained a preponderance of basophilic elements.

2 The changes in renal function, circulatory system, edema, anemia, etc., were in degree and rate of progress, typical of an actively progressing nephritis. The pituitary anomaly had no obvious effect on the character or course of the nephritic syndrome.

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COMPLETE AURICULOVENTRICULAR DISSOCIATION DUE TO DIGITALIS, WITHOUT SYSTEMIC EFFECTS OF OVERDOSAGE: REPORT OF A CASE*

By THOMAS J. DRY, M.B., and GILES A. KOELSCH, M.D.
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THE protean manifestations of digitalis intoxication, which consist of gastrointestinal disturbances, color vision phenomena and digitalis delirium, are well recognized. A group of electrocardiographic changes, including coupled beats, extrasystoles, ectopic rhythm, and conductive defects of varying degrees, is not infrequently encountered. It has long been known that changes in the T-wave (one variety of which is characteristic of digitalis poisoning) occur with great frequency and that they may be noted before any digestive disturbances have

† There was an excess of basophilic elements in the anterior hypophysis in this case also. Page (1936) did not find any clinical signs or symptoms suggestive of pituitary dysfunction in his case, however.

* Submitted for publication May 7, 1937.

occurred. It is doubtful, however, whether it is universally recognized that certain instances of gross overdigitalization, which are characterized by profound electrocardiographic changes, may not be associated with any of the usual systemic effects.

CASE REPORT

A woman, 39 years of age, who was rather high-strung and nervous, came to The Mayo Clinic in June 1936 complaining of palpitation on exertion or excitement. This had been present since she had been a girl. There was no history of rheumatic fever or of hypertension. She had gone through three pregnancies without incident, it had required an unusual amount of exertion to bring on breathlessness. There was no history of dependent edema, nor had she been subject to syncopal seizures. Because of the symptoms referable to her heart, one tablet of digitalis had been administered three times daily for about five weeks before her registration at the clinic and she had continued to take this dose until a few days before her first examination at the clinic.

For 10 years she had been troubled with epigastric bloating and fullness, which had not had any definite quantitative or qualitative relationship to the ingestion of food. During the few weeks prior to her visit to the clinic, these symptoms had, if anything, improved. There had not been any anorexia, nausea, vomiting, or disturbance of the bowels. Physical examination did not reveal any abnormality except an arrhythmia, the nature of which is disclosed by the electrocardiographic studies. The value for the systolic blood pressure was 110 millimeters of mercury and that for the diastolic was 64 millimeters. The pulse rate, when the patient was first seen, was 80 beats per minute. It was noted that pressure on the carotid sinus promptly caused a marked slowing of the pulse rate. There was not any enlargement of the heart or any bruits. The results of laboratory studies, including urinalysis, blood counts, roentgenographic studies of the heart and lungs, gall-bladder, and stomach, were all reported as normal. It was possible to keep the patient under observation for only a matter of 11 days. During this time, electrocardiographic studies, which were repeated on several days (figure 1a, b and c), revealed a gradual transition toward normal. Pressure over the carotid sinus caused very definite bradycardia, but as the digitalis effects wore off, it was no longer possible to elicit this phenomenon.

COMMENT

The absence of any probable basis for cardiac disease, the nature of the symptoms and their duration, the absence of the usual features associated with complete heart block, and the history of administration of relatively large doses of digitalis led us to suspect the true nature of the trouble. With our present incomplete knowledge of the carotid sinus reflex, we are unable to explain the peculiar electrocardiographic observations noted when pressure is applied over the carotid sinus, but we wish to record them as interesting findings.

It is frequently difficult to gauge the approximate amount of the drug administered in a given period of time from the history, and it is possible that certain patients have a heightened cardiac susceptibility to even small amounts of drugs which belong to the digitalis group. Yet, in the cases in which digitalis is clearly indicated, these changes, except perhaps for diphasic or inverted T-waves in the great majority of cases, fail to occur until clinical effects of overdosage become apparent.

Obviously, if an electrocardiographic record taken prior to the institution of digitalis therapy is not available under these circumstances, these changes

might be erroneously interpreted as indicative of severe myocardial damage, the result of organic heart disease. Moreover, should the patient present either clinical evidence of, or a background which may constitute the basis for, cardiac disease, the seriousness of that disease may be unnecessarily overestimated.

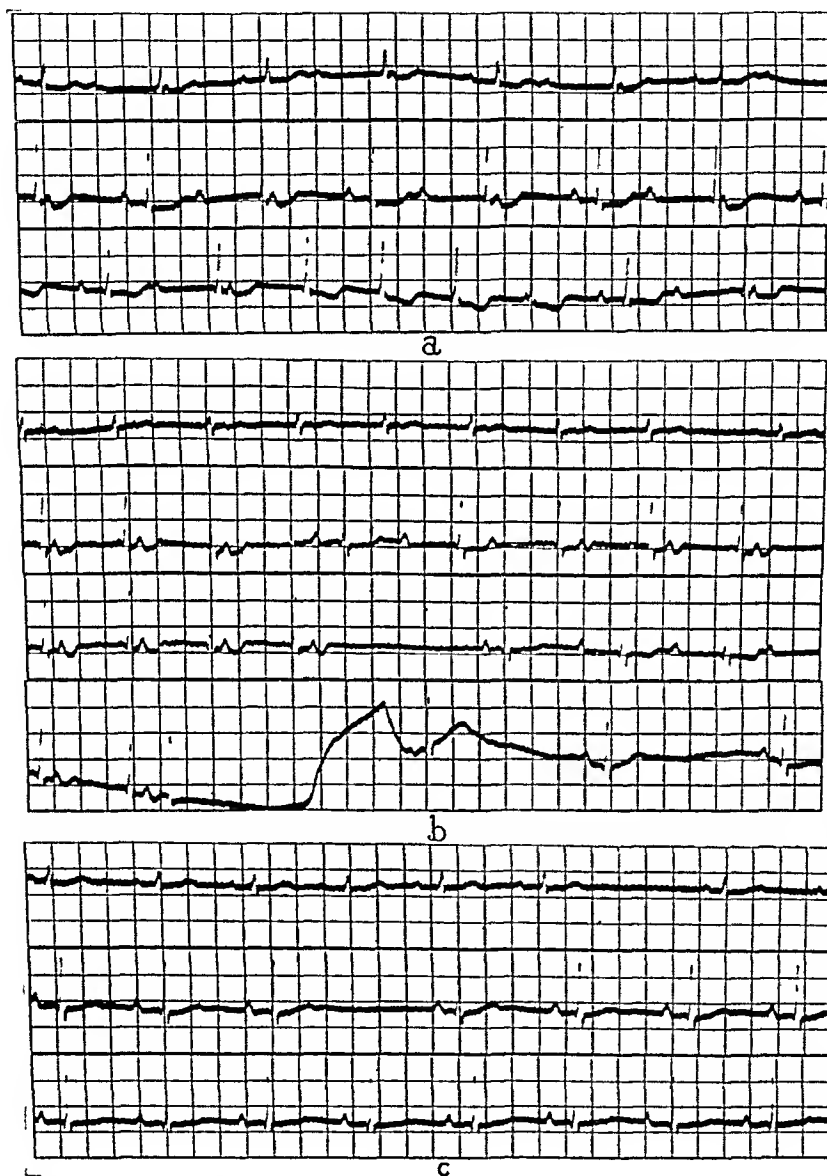


FIG 1a Electrocardiogram (June 18, 1936) showing complete auriculoventricular dissociation, the auricular rate is 106 and the ventricular rate is 70 per minute, one may note a short series of nodal premature contractions and inversion of the T-waves in Leads II and III, b, electrocardiogram (June 22, 1936) showing a rate of 80, nodal rhythm, periods of auriculoventricular dissociation, and a dropped beat, carotid pressure caused definite slowing of the heart, c, electrocardiogram (June 25, 1936) showing a rate of 65 sinus rhythm, sinoauricular block with upright T-waves in Leads I and II, and a diphasic T-wave in Lead III

Errors in diagnosis in these circumstances can be avoided if a sufficiently careful inquiry is made into the cardiac status of the patient prior to the institution of treatment. It is usually possible to ascertain whether there is any reason why organic heart disease might be present, such as the existence or history of hypertension, syphilis or coronary disease, including myocardial vascular accidents. Valvular lesions, both acquired and congenital, can be ascertained or ruled out by physical examination, again, one's suspicions should be aroused when the particular electrocardiographic pattern does not fit the pathologic picture (if any) presented by the patient.

This is well illustrated by the case of a woman, aged 42 years, who had a history of hypertension, but who had reasonably good tolerance to exertion. There was no cardiac enlargement and no history or evidence of congestive heart failure. She never had experienced pain which could in any way be labelled as anginal. The remarks noted at the time the patient was first seen were as follows: "The electrocardiographic changes are out of all proportion to the symptoms in spite of the hypertension." Furthermore, unless this patient had

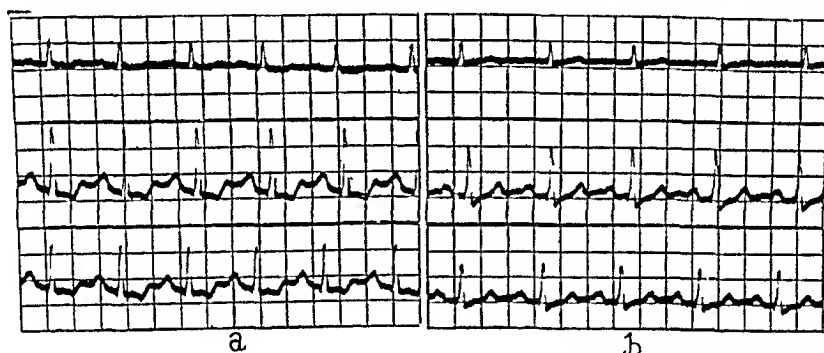


FIG 2a Sinus rhythm with inversion of T-waves in Leads II and III, b, a normal electrocardiogram

had a previous myocardial infarct in the posterior basal part of the left ventricle (and we were sure that she had not, from the history), if any changes in the T-wave were present as a result of the hypertension, they should have been prominent in Leads I and II. Rheumatic heart disease with right ventricular strain might cause such changes in the electrocardiogram but this could readily be excluded by physical examination. After discontinuing all of her medications, one of which was digitalis, the electrocardiogram reverted completely to normal (figure 2a and b). It is important to remember also that the effects of digitalis on the electrocardiogram may persist for as long as three weeks after administration of the drug is discontinued.

Digitalis has its clear-cut indications in auricular fibrillation or as an adjunct to quinidine in auricular flutter, in certain cases of congestive heart failure, with or without an ectopic rhythm, and in certain instances in which the episodes of acute ventricular failure characterized by nocturnal dyspnea are not relieved by rest alone. The indiscriminate administration of an otherwise unequalled cardiac remedy for "all that ails" is to be strongly deprecated, particularly in those instances in which a frank discussion and a simple explanation of the mechanism of a variety of functional symptoms referable to the cardiovascular

system will suffice to reassure the patient and to relieve his mind as to any seriousness of their significance. Moreover, if digitalis therapy should be deemed necessary, the physician who prescribes this drug assumes the responsibility not only of administering it in amounts large enough to produce the desired pharmacologic effects, but also in amounts which shall not exceed the limits of physiologic safety.

SUMMARY

A case is reported in which too large a dosage of digitalis caused complete auriculoventricular dissociation. Despite profound electrocardiographic changes, systemic toxic effects were entirely absent. In this particular instance, the symptoms referable to the cardiac system were not the result of organic heart disease, and digitalis, far from being indicated in the management of the condition, might readily have led to confusion in its diagnosis and an unwarranted seriousness in the prognosis.

EDITORIAL

PROTAMINE INSULIN AND DIET IN DIABETES MELLITUS

BEFORE enumerating methods for achieving the best regulation of the diabetic regimen it is important to marshal the available facts that throw light on this phase of the disease. Only in this way can we clarify our objective and estimate the degree of success attained.

Adequate regulation of a patient with diabetes mellitus has been thought for a long time to consist in balancing the diet and insulin in a way that maintains the urine free from sugar, avoids periods of hyperglycemia, and at the same time avoids insulin reactions. In many patients this degree of regulation has not been possible and the ones who are difficult to regulate often vacillate precipitously from insulin shock to diabetic coma. With the use of protamine zinc insulin smooth adjustment occasionally is even more difficult and some of the more critical physicians who are especially interested in diabetes mellitus say that they have never seen a patient "regulated" on one daily dose of protamine insulin.

Some specialists in the treatment of diabetes advocate a high carbohydrate diet with one morning dose of protamine insulin which, in severe cases, may or may not be augmented by a simultaneous dose of regular insulin and they more or less ignore the presence of sugar in the urine up to as much as 40 gm. in 24 hours. It is obvious that such a regimen includes not only glycosuria but periods of marked hyperglycemia. Mosenthal¹ in 1935 expressed the belief that the damage done to the patient with diabetes mellitus occurred not from the abnormally high level of blood sugar but rather from the long continued effects of glycosuria with its attendant polyuria. In considering Mosenthal's hypothesis we can say in the first place that patients with renal glycosuria may excrete large quantities of sugar in the urine over periods of years without any evidence of damage resulting therefrom except undernutrition. This fact justifies some doubt as to the correctness of Mosenthal's principle. There is still the possibility that polyuria in a patient with true diabetes is more serious than in one with merely a low renal threshold for glucose but convincing evidence is lacking. In the second place there is fresh evidence to suggest that a patient whose urine is sugar free and whose blood sugar is constantly within normal limits may still not be properly regulated if the depots of glycogen, particularly in the liver, are not maintained at a normal level. It is clearly shown by de Wesselow and Griffiths² that it is impossible to classify patients as permanently insulin sensitive or insulin resistant. Patients who are insulin resistant become sensitive to insulin by carefully balancing a high carbohydrate intake.

¹ MOSENTHAL, H. O. Hyperglycemia, evaluation in treatment of diabetes mellitus, Jr. Am. Med. Assoc., 1935, cv, 484-488.

² THOMAS, H. M., JR. The renal threshold for glucose, ANN. INT. MED. (In press.)

³ DE WESSELOW, O. L. V., and GRIFFITHS, W. J. Insulin resistance in diabetes mellitus and the effect of dietary carbohydrate, Quart. Jr. Med., N. S., 1938, vii, 17-28.

with adequate doses of insulin. Bridge⁴ has come to the same conclusions from his studies on the action of insulin on glycogen reserves. He found in rabbits that large doses of insulin given during the course of glucose infusion serve to deposit more glycogen in the muscle and less in the liver but do not result in increasing the respiratory quotient. He has also found that after a poorly regulated patient with diabetes mellitus has been on a controlled high carbohydrate regimen for some time the respiratory quotient does become higher. Bridge, like de Wesselow and Griffiths, believes that this is brought about by an increase in the amount of hepatic glycogen and an improvement of glycogen metabolism in the liver. These findings are in accord with the statements of many clinicians that their patients are very much better while on a high carbohydrate diet.

It is impossible to say at present whether hyperglycemia and glycosuria are harmful if in other respects the sugar metabolism in the body is essentially normal. We can say, on the other hand, that severe insulin shocks and possibly repeated mild attacks of hypoglycemia are harmful and in the face of arteriosclerotic coronary or cerebral arteries are actually dangerous.

For the past decade several clinics both abroad and in this country have prescribed very high carbohydrate diets amounting to 300 or 400 gm of carbohydrate a day. Most clinics refuse to be quite so radical but practically all have been influenced to a greater or less extent. The general experience with diets containing between 150 and 225 gm of carbohydrates a day is that the patient feels better, likes his food better, needs little or no more insulin than on a lower diet and has fewer insulin reactions. It is interesting to find a rational explanation of these beneficial results in an improved hepatic glycogen metabolism with coincidental improvement in insulin utilization.

Protamine insulin introduces new problems of regulation. Since the absorption rate is so much slower than regular insulin the full effect from an injection is not obtained for five or six hours. After that the effect is more or less constant for the next 18 or 20 hours although the injected insulin is more rapidly utilized if food is taken than when it is not. Hypoglycemic reactions are usually encountered in the early morning hours after the long period of fasting during sleep. These facts necessitate certain changes in the dietary regime. Since the rate of absorption of protamine insulin is thought to be more uniform than the rate of production of endogenous insulin of a normal individual it is well to supply the carbohydrate in somewhat smaller amounts at shorter intervals. The indications may be met by starting the day with a small carbohydrate meal and by supplying some carbohydrate just before retiring at night. Another satisfactory formula for distributing the carbohydrate during the 24 hours is to divide

⁴ BRIDGE, E. M. The action of insulin on glycogen reserve, Bull Johns Hopkins Hosp, 1938, LXII, 408-421.

BRIDGE, E. M. and WINTER, E. A. Diabetes, carbohydrate combustion and insulin action, Bull Johns Hopkins Hosp (In press)

the total amount into $\frac{1}{6}$, $\frac{2}{6}$, $\frac{2}{6}$, for the three meals and then to subtract 10 gm from each meal and present it in a convenient form three hours after meals

If, then, one subscribes to the principle that the diet must contain enough carbohydrate to keep the hepatic storehouse of glycogen at a high level it is logical to place the lowest limit of carbohydrate in the diet at 150 gm a day. If the patient's caloric requirement permits, this amount may be increased to 200 gm or 225 gm daily. It is customary to keep the protein at the lowest level which is consistent with nitrogen balance and the fat low enough to prevent the patient from gaining weight or, if already overweight, to bring about a gradual loss of weight. Blood sugar estimations at intervals during the day and night often show normal variations when suitable protamine insulin dosage is given.

Unusual exercise is frequently followed by hypoglycemia. However, patients become familiar with this consequence of unusual exertion and learn to forestall severe attacks by eating extra bread or fruit or some other readily available carbohydrate. Where an amount of exercise customary to the patient is followed by a hypoglycemic reaction, reduction of the protamine insulin dosage is indicated but after the reduction glycosuria must be watched for more carefully than before.

Moderate variations in blood sugar levels are unimportant and extreme ones make themselves evident to the watchful patient in a way that enables him to change his single dose of insulin or his diet to suit the situation. It has been shown that excellent regulation with protamine insulin can be obtained by proper dietary adjustment of an adequately high carbohydrate intake. The patient not only is happier and feels very much better on this than on any other regimen but also the metabolic processes more nearly approach normal.

H M T, JR

REVIEWS

Protoformotherapy in Treatment and Prevention By N E ISCHLONDSKY 237 pages, 15 × 26 cm H Kimpton, London 1937 Price, \$5 00

The author has combined a series of lectures delivered before the Egyptian Medical Association of the University of Cairo into the above volume "Protoformotherapy," as defined, "is a basic conception, the most characteristic feature of which is the widest application of synthesis in the interpretation of morbid phenomena" The idea is based upon the supposed stimulation of the natural protective capacities of the organism by injection of an incret derived from embryos during the third and fourth month of gestation The incret is advocated by the author for the treatment of innumerable disease states pulmonary tuberculosis, chronic nephritis, endocrine disturbances and epileptiform states, constitute only a small number In support of the extraordinary results obtained in the treatment of these conditions, the author offers extremely inadequate case reports An inadequacy which in view of the monumental claims made by the author, throws great doubt upon the value of the work

J E B

In the Realm of Mind By CHARLES S MYERS, Psychologist 251 pages, 12 × 18 cm Cambridge University Press, London, Macmillan Co, New York 1938 Price, \$2 50

This book is made up of nine chapters on the applications and implications of psychology in the relationships of human society The fourth chapter will be of especial interest to medical readers as it is entitled "A Psychological Regard of Medical Education," and is a reprint of the Bradshaw Lecture, delivered before the Royal College of Physicians

The author feels that our present system of medical education tends to turn out specialists rather than clinicians because medical education is "almost wholly in the possession of specialists, each with his own vested interests, each maintaining the supreme importance of a full knowledge of his subject for the medical student, and strenuously opposing any reduction in the time devoted to it" He makes a plea that the future clinician should receive first a more general education in the whole range of medicine and surgery before he visits the "too water-tight departments of the specialist physicians and surgeons expressly to learn about the rarer diseases—but specialization should follow, not form part of, elementary medical education"

In the other chapters of this book the reader will find many thought provoking statements, and no doubt will agree with the author that "psychology unquestionably offers great help in the choice of a career"

J L McC

A Diabetic Manual By EDWARD L BORTZ, M D 222 pages, 14 × 20 5 cm F A Davis Co, Philadelphia 1936

Five authors have contributed to Dr Bortz's Manual for Diabetics There is an interesting foreword by Dr George Morris Piersol There is already a considerable number of manuals for diabetics available, but the present one presents many good features It is very readable and many of the sections are outstanding, for example those upon the "Administration of Insulin" and the "Care of the Feet" The chapter given up to the associated condition, obesity, is interesting and instructive

It appears as if the use and dangers of protamine-zinc-insulin were not given adequate discussion. It is questionable whether it is justifiable to say that "certain cases of renal glycosuria develop a mild form of diabetes in later years." There is some question also whether certain parts of the manual are not more suited for the comprehension of physicians than for that of patients.

J S E

A Textbook of Medicine Edited by RUSSELL L. CECIL, A B, M D, Sc D, Associate Editor for Diseases of the Nervous System, FOSTER KENNEDY, M D, F R S E. Fourth Edition, revised. 1614 pages, 17 × 25 cm. W B Saunders Co., Philadelphia. 1937. Price, \$9.00.

There can be no doubt that the new edition of this text will establish even more firmly its rapidly growing popularity. One hundred and forty authors have contributed to it, and the reader cannot but be impressed by the excellent editing and arrangement of the work—a difficult undertaking with such a large number of writers. The style is uniformly clear and concise and at the same time very readable and interesting.

Nine additional subjects have been introduced to the present volume. Twenty-nine subjects have been rewritten by authors new to the Textbook, partly because of the death of some of the former contributors, and partly because of a new editorial policy of retiring older writers and replacing their work by that of a younger group of teachers. The Editor, in his preface, regrets the loss of some of the articles, but his good judgment in selecting new contributors has made the present edition one of the best textbooks available, both for the student and practitioner.

T N C

COLLEGE NEWS NOTES

GIFTS TO THE COLLEGE LIBRARY

Grateful acknowledgment is made of the receipt of the following donations to the College Library

Books

- Dr F M Pottenger (Fellow and Regent), Monrovia, Calif—an autographed copy, Fifth Edition, "Symptoms of Visceral Disease",
Dr Emanuel M Josephson, New York, N Y—"Glaucoma and Its Medical Treatment with Cortin"

Reprints

- Dr George E Baker (Associate), Casper, Wyo—3 reprints,
Dr Karl F Eschelman (Fellow), Buffalo, N Y—1 reprint,
Dr James O Finney (Associate), Gadsden, Ala—3 reprints,
Dr William Freeman (Fellow), Worcester, Mass—1 reprint,
Dr Hyman I Goldstein (Associate), Camden, N J—2 reprints,
Dr Irving Gray (Fellow), Brooklyn, N Y—26 reprints,
Dr Jacob Gutman (Fellow), Brooklyn, N Y—Second Series Supplement to "The Modern Drug Encyclopedia",
Dr J Morrison Hutcheson (Fellow and Governor for Virginia), Richmond, Va—1 reprint,
Dr Vincent W Koch (Fellow), Janesville, Wis—1 reprint,
Dr Manfred Kraemer (Fellow), Newark, N J—2 reprints,
Dr Charles E Lyght (Associate), Northfield, Minn—4 reprints,
Dr Arthur M Master (Fellow), New York, N Y—20 reprints,
Dr William B Rawls (Fellow), New York, N Y—1 reprint,
Dr David Salkin (Associate), Hopemont, W Va—1 reprint,
Dr Benjamin Saslow (Associate), Newark, N J—1 reprint,
Dr Jacob Schwartz (Associate), Brooklyn, N Y—1 reprint,
Dr Christopher C Shaw (Associate), Bellows Falls, Vt—7 reprints,
Dr Frederick R Taylor (Fellow), High Point N C—Chapter VI-B and Chapter XIV-E, Oxford Loose-Leaf Medicine,
Dr Edward G Thorp (Fellow), Boston, Mass—5 reprints,
Dr Walter H Watterson (Fellow), La Grange, Ill—1 reprint
Dr Samuel Weiss (Fellow), New York, N Y—3 reprints
Dr M C Pincoffs (Fellow), Baltimore, Md, contributed a reprint by Dr Lewellys F Barker (Fellow), Baltimore, Md, on "Comments on Tetanus," the original article appearing in Volume I, No 4, February, 1921, of the "Annals of Medicine," the original official publication of the College

NEW LIFE MEMBERS

Dr Emanuel Klaus (Fellow), Cleveland, Ohio, and Dr Harry W Coffin (Fellow), Los Angeles, Calif, have become Life Members of the American College of Physicians making a total of one hundred and one members who have subscribed to Life Membership, four of whom are now deceased

MARYLAND CHAPTER OF THE COLLEGE

On April 19 Fellows of the College residing in Maryland held a meeting under the chairmanship of Dr Henry M Thomas, Jr (Fellow and Governor of the College for Maryland), at which it was decided to establish a so-called Maryland Chapter of the members of the College Dr Sydney R Miller (Fellow), Baltimore, was elected chairman for the first year It is planned to have at least two meetings a year and other meetings if special circumstances arise

Through arrangements by the American Heart Association, New York City, leading British and American physicians, 6,000 miles apart, conferred via the radio on Rheumatic Heart Disease, the greatest menace to child health This conference the first international broadcast on any health problem, was heard over the National Broadcasting Company, WEAf and the Red Network on May 2, in connection with the observance of National Child Health Day The conference was opened by Lord Thomas Jeeves Horder, Physician-in-ordinary to the King of England, from London Dr Homer F Swift of the Rockefeller Institute, New York City, and Dr T Duckett Jones of the House of the Good Samaritan, Boston, spoke from Atlantic City, where they were attending the convention of the American Society for Clinical Investigation Dr William J Kerr, President of the American College of Physicians and of the American Heart Association, took up the discussion from San Francisco

Under the Presidency of Dr Alphonse McMahon (Fellow), St Louis, the American Therapeutic Society held its Thirty-Ninth Annual Meeting at the Waldorf-Astoria Hotel in New York City April 1-2 1938 Among its officers were Dr Harold S Davidson (Fellow), Atlantic City, and Dr Hal McCluney Davison (Fellow), Atlanta, Ga, Vice Presidents, Dr Oscar B Hunter (Fellow), Washington, D C, Secretary, Dr Henry H Turner (Fellow), Oklahoma City, Treasurer On its Council of fifteen members all but four are Fellows of the College All but a very few of the Fellows and Active Members of this Society are Fellows of the College The majority of those presenting papers at the New York meeting were also Fellows of the College Dr F M Pottenger (Fellow and Regent), Monrovia, Calif, was a speaker of the evening at the annual dinner and President's Reception Dr Reynold Webb Wilcox, deceased, first president of the American College of Physicians, was the second president of the American Therapeutic Society

DR WILLIAM G HERRMAN RECEIVES RUTGERS AWARD

Dr William G Herrman (Fellow), Asbury Park N J, was the recipient of the Rutgers' Award, a medal of honor by Rutgers University for his outstanding service to society in the field of medicine, and for his loyalty to his Alma Mater, from which he graduated in 1912 The presentation was made on February 22, 1938, at a dinner celebrating the annual Alumni Day by the College The medal was presented by Dr Robert Clothier, President of the University

Citation

" Here, in the presence of your fellow-alumni, I want to pay the University's tribute to you for your services, both to your University and to your profession Voltaire wrote 'But nothing is more estimable than a physician who, having studied nature from his very youth, knows the properties of the human body,

the diseases which assail it, the remedies which will benefit it, exercises his art with caution and pays equal attention to the rich and poor' In war and in peace, you have practiced your profession with achievement and with promise of yet greater achievement to come, especially with reference to the application of radiology and roentgenology to medicine In recognition of your attainments, you have been made a Fellow of the American College of Physicians and of the American College of Radiology—and only recently the President of the Medical Society of New Jersey

"Yet, despite the exacting demands of your professional work, you have always found time to wear a trail back to the campus where you studied in those years prior to 1912 Your counsel and support have always been available to your Alma Mater It is appropriate that, with the authority of the Trustees, I should confer on you today the Rutgers University Award This medal, which I hand you, is the visible token of our tribute"

Dr Hilton S Read (Fellow), Atlantic City, is the chairman of the Welfare Committee (executive body) of the Medical Society of New Jersey

The Desert Sanatorium of Southern Arizona, located at Tucson, is conducting a special program and special low rates for arthritics from May 15 to October 15, 1938 The Sanatorium does not stress nor exploit any particular method of treatment of arthritis but, following out good medical practice, bases therapy upon the diagnostic findings in each case

Dr Roland Davison (Fellow) is the Medical Director and Dr C W Mills (Fellow) is the Chief Visiting Physician

Dr Joseph Hajek (Fellow) and Dr Thomas T Mackie (Fellow), both of New York City, were Chairman and Secretary, respectively, of the Section on Medicine of the New York Academy of Medicine for the year 1937-38

Dr Hajek contributed a paper on "The Cardiogram in Health and Disease" on the Scientific Program of the South Brooklyn Medical Society Meeting, April 14, 1938

Dr Ross M Lymburner (Fellow), Hamilton, Ontario, spoke on "The Treatment and Later Management of Coronary Thrombosis" before the annual meeting of the Ontario Medical Association, held at the Royal York Hotel, Toronto, Ontario, May 2 to 6

Dr H I Spector (Associate), St Louis, has received a joint invitation from the Kansas State Medical Society, Kansas State Board of Health and the Kansas Tuberculosis and Health Association to lecture to the medical societies of several cities of the State of Kansas on the subject of "Symptoms Diagnosis and Differential Diagnosis of Early Pulmonary Tuberculosis" He was the guest of the Leavenworth County Medical Society on April 18, of the Franklin County Medical Society in Ottawa on April 19, of the Sedgwick County Medical Society in Wichita on April 21, and of the Central Kansas Medical Society in Russell on April 22

On March 10, 1938, the Morgan County (Illinois) Medical Society held its Fiftieth Anniversary Celebration Meeting, honoring Dr Frank Parsons Norbury (Fellow), of Jacksonville, Ill. The speakers included Hon A L Bowen, Director of the Department of Public Welfare, State of Illinois, Dr Tom B Throckmorton (Fellow), Des Moines, Iowa, and Dr Charles L Patton, F A C S, Springfield, Ill

On February 8, 1938, members of the American College of Physicians in Puerto Rico gave a farewell dinner to Dr Ramon M Suarez, Governor of the College for Puerto Rico, preceding his sailing to participate in the postgraduate course offered under the auspices of the College at Harvard University. Among the Puerto Rico members present were Dr Ramon M Suarez, Dr Carlos E Muñoz MacCormick, Dr Guillermo Marques, Dr Antonio Ortiz, Dr Luis Morales, Dr Cesar Dominguez, Dr R Rodriguez-Molina, Dr Enrique Koppisch, Dr Jose Landron, Dr O Costa-Mandry and Dr Jose Garrido Collazo.

Dr Suarez later attended the Annual Session of the College at New York City, taking his place on the Board of Governors as the representative from Puerto Rico. On behalf of the Fellows and Associates of the College in Puerto Rico, Dr Suarez presented a set of resolutions signed by all the Puerto Rico members, inviting the College to come to Puerto Rico on a post-convention cruise to inspect their work and institutions.

Dr Warren F Kahle (Fellow), 17 N Chatsworth Avenue, Larchmont, N Y, has prepared a very interesting and instructive talking slide film on the subject, "Treating Pneumonia." This film has but recently been completed, and Dr Kahle has expressed his willingness to loan it to Fellows of the College. It requires twenty-three minutes, and is a combination of still and talking film. The apparatus for showing the film is available in practically every community. The film and the record may be loaned, or Dr Kahle will show it personally to groups not too far removed from Larchmont.

The Chicago Tumor Institute opened March 21, 1938, offering consultation service to physicians in the diagnosis and treatment of cancer and radiation facilities for cancer patients. The Institute also proposes to conduct research and to offer training to physicians who may wish to qualify as specialists in the study and treatment of this disease. The scientific committee consists of Max Cutler, M D, Director, Sir G Lenthal Cheatle, F R C S, Henri Coutard, M D, Arthur H Compton, Ph D and Ludwig Hektoen, M D.

Dr A A Leonidoff (Associate), Poughkeepsie, N Y, addressed the Dutchess County Psychiatric Society March 18, 1938, on "Control of Tuberculosis in the Hudson River State Hospital."

Dr Arthur J Logie (Associate), Jacksonville, Fla, addressed the Polk County Medical Society at Lakeland, Fla, on January 12, 1938, the Suwannee River Medical Society at Mayo, Fla, on February 11, 1938, the Florida Tuberculosis Association at Orlando, Fla, on April 26, 1938, and the Duval County Medical Society at Jacksonville, Fla on May 2, 1938. His subject was "The Value and Significance of the Tuberculin Test."

Dr M Coleman Harris (Fellow), New York City, has been advanced to Adjunct Professor of Medicine and Head of the Department of Allergy at the New York Polyclinic Hospital. Because of the added duties of this new appointment, he has resigned his appointment at Roosevelt Hospital

Under the presidency of Dr Edward S Sledge (Fellow) Mobile, the Medical Association of the State of Alabama held its annual meeting in Mobile, April 19-21. Among members of the College who contributed to the program were Dr John H Musser (Fellow), New Orleans, "Treatment of Organic and Inorganic Diseases of the Stomach", Dr Oscar W Bethea (Fellow), New Orleans, "The Pneumonias", and Dr Joe H Little (Associate), Mobile, "Progress in the Treatment of Diabetes"

Dr Thomas M McMillan (Fellow), Philadelphia, delivered the Jerome Cochran Lecture on "An Optimistic View of Some Problems of Heart Disease"

Dr Joseph Yampolsky (Fellow), Atlanta, Ga addressed the Thirteenth Annual Session of the Alabama Pediatric Society, April 18, on "A Comparative Review of the Drugs Used in the Treatment of Syphilis"

Dr Elliott P Joslin (Fellow), Boston, addressed the Chicago Medical Society April 6 on "Present Conceptions of Diabetes Mellitus"

Dr Alan Brown (Fellow), Toronto, Ont, addressed the Northern Tri-State Medical Association in Findlay, Ohio, April 12, on "Some Common Disturbances in Children Frequently Handled Incorrectly"

Dr M Herbert Barker (Associate), Chicago, addressed the Arkansas Medical Society at Texarkana April 18-20 on "Phases of Renal Edema and Their Treatment"

Dr Benjamin W Black (Fellow), Oakland and Dr Clifford W Mack (Fellow), Livermore, have been appointed to a committee to aid the California State interim committee on state hospitals, authorized by the legislature to study hospitalization of the insane

Dr Logan Clendenning (Fellow), Kansas City, Mo, delivered a public lecture on "The Care and Feeding of Humans" under the auspices of the Chicago Medical Society at the Goodman Theater in Chicago on April 13

Dr William Devitt (Fellow), Allenwood, Pa, was elected president of the Pennsylvania Tuberculosis Society

Dr Udo J Wile (Fellow) Ann Arbor, addressed the Allegheny County (Pa) Medical Society at Pittsburgh, April 19, on "Syphilis in Relation to Surgical Problems"

Dr John Zahorsky (Fellow), St Louis, addressed the one hundred and fifth annual meeting of the Tennessee State Medical Association at Nashville, April 12-14, on "The Newborn Baby in the Hospital"

Among guest speakers at the annual meeting of the Texas Tuberculosis Association held in El Paso, April 15-16, were Dr Jay Arthur Myers (Fellow), Minneapolis, president of the National Tuberculosis Association, and Dr Lewis J Moorman (Fellow), Oklahoma City

Dr James N Williams (Associate), Richmond, Va, addressed the sixty-second annual meeting of the American Association on Mental Deficiency at Richmond, April 20-23, on "Emotional Education of Children"

Stanford University School of Medicine, San Francisco, has inaugurated a course of popular medical lectures Among Fellows of the College who have recently contributed are Dr Walter W Boardman (Fellow), San Francisco, "Conditions of the Mouth in Relation to Disease", Dr William J Kerr (Fellow and President), San Francisco, "Forty, Fat and Florid and Heading for Circulatory Failure", and Dr Dwight L Wilbur (Fellow), San Francisco, "Vitamin Facts and Fallacies"

Dr James S McLester (Fellow), Birmingham, Ala, delivered the Ewing Fox Howard Oration on "Causes and Effects of Hypertension" before the seventy-first annual session of the Mississippi State Medical Association at Jackson, Miss, April 19-21

Under the presidency of Dr Homer Davis (Fellow), Genoa, Nebr, the Nebraska State Medical Association held its annual convention at Lincoln, April 26-28

Dr Arthur C Christie (Fellow), Washington, D C, delivered the annual J Chalmers DaCosta Foundation Lecture on "Comprehensive Planning for Medical Care—the Physician's Responsibility," March 30, before the third annual Post-graduate Institute of the Philadelphia County Medical Society Dr Rufus S Reeves (Fellow), Philadelphia, was chairman of the committee that organized the Institute

Dr Bernard L Wyatt (Fellow), Tucson, Ariz, was recently awarded a medal from the Comité National de Défense contre la Tuberculose in France in appreciation of his work in tuberculosis during the World War

Dr Robert A Hare (Fellow), Santa Barbara, Calif, was recently appointed Medical Director of the Washington Sanatorium and Hospital, Takoma Park, Washington, D C

Dr Thomas Parran (Fellow), Surgeon General of the U S Public Health Service, was recently awarded a medal by the "Parents Magazine" for outstanding service to children

Dr Cyrus C Sturgis (Fellow), Ann Arbor, addressed the eighty-seventh annual session of the Iowa State Medical Society at Des Moines, May 11-13, on "Diseases Associated with Changes in the Red Blood Cells"

Dr Ray M Balyeat (Fellow), Oklahoma City, addressed the Louisiana State Medical Society at New Orleans, May 2-4, on "Common Allergic Manifestations Encountered by the General Practitioner"

Dr Leonard G Rowntree (Fellow), Director of the Philadelphia Institute for Medical Research, was the recipient of the annual Strittmatter Award, a gold medal, at a meeting of the Philadelphia County Medical Society on April 13, the award being made in recognition of Dr Rowntree's work on the thymus gland, cancer and arthritis

Dr Eugene F DuBois (Fellow) and James D Hardy, New York, addressed the National Academy of Sciences at Washington, D C, recently on "Relationship of Humidity to Evaporation of Sweat"

Dr William R Houston (Fellow), Austin, Texas, was the banquet speaker at the forty-first annual meeting of the American Gastro-Enterological Association at Atlantic City, May 2-3, his subject being, "Our Relations with the Orient" Dr Houston also addressed the Medical Society of the District of Columbia at the public meeting in connection with its annual scientific assembly May 4-5 on "Western Medicine in China"

Dr Edward A Strecker (Fellow), Philadelphia, addressed the one hundred and thirty-second annual meeting of the Medical Society of the State of New York, held in New York City, May 9-12, on "The Importance of Psychology in the Practice of Medicine"

Dr Paul A O'Leary (Fellow), Rochester, Minn, addressed one of the sections on "Significance of Asymptomatic Neurosyphilis"

The eighty-fifth annual session of the Medical Society of the State of North Carolina was held at Pinehurst May 2-4, under the presidency of Dr Wingate M Johnson (Fellow), Winston-Salem

Among the guest speakers was Dr Edward A Strecker (Fellow), Philadelphia, "Functional Illness and the Medical Psychology Needed by the Practitioner in Its Treatment"

A memorial tablet to the late Dr William Duffield Robinson (Fellow), was unveiled by the trustees of the Philadelphia Institute for Medical Research at its building at the Philadelphia General Hospital on April 7 Dr Robinson was active in the formation of the Institute He died in 1931

Dr James B Collip (Fellow), Montreal, Que, addressed the Philadelphia Pediatric Society April 12 on "Anterior Pituitary Hormones"

Dr John A Kolmer (Fellow), Philadelphia, addressed the seventy-second annual session of the Texas State Medical Association at Galveston, May 10-12, on "Syphilis"

The Congress of American Physicians and Surgeons held its Semi-Centenary Meeting at Atlantic City, May 3-4, 1938, under the presidency of Dr James B Herrick (Fellow and 1st Vice President), Chicago. The Congress is held every five years. The component associations and societies include the American Otological Society, American Neurological Association, American Gynecological Society*, American Dermatological Association*, American Laryngological Association, American Surgical Association, American Clinical and Climatological Association, Association of American Physicians, American Association of Genito-Urinary Surgeons, American Orthopedic Association, American Pediatric Society*, American Association of Pathologists and Bacteriologists. However, those societies marked with an asterisk did not hold meetings with the Congress this year.

Among the officers of the Association of American Physicians were Dr George R Minot (Fellow), Boston, President, Dr Eugene F DuBois (Fellow), New York, Vice President, Dr Hugh J Morgan (Fellow), Nashville, Tenn, Secretary, Dr William S McCann (Fellow), Rochester, N Y, Treasurer, Dr Francis G Blake (Fellow and Governor), New Haven, Conn, Recorder, Dr Gerald B Webb (Fellow), Colorado Springs, Dr Louis Hamman (Fellow), Baltimore, Dr James H Means (Fellow and Ex-President), Boston, Dr George Blumer (Fellow), New Haven, Conn, and Dr Warfield T Longcope (Fellow), Baltimore, Members of the Council, Dr O H Perry Pepper (Fellow and President-Elect), Philadelphia, Delegate to the Executive Committee of the Congress, Dr Ernest E Ions (Fellow), Chicago, Alternate Delegate, Dr Richard A Kern (Fellow), Philadelphia, Alternate Committeeman.

Among the officers of the American Clinical and Climatological Association were Drs John H Musser (Fellow), New Orleans, and James J Waring (Fellow), Denver, Vice Presidents, Dr Francis M Rackemann (Fellow), Boston, Secretary and Treasurer, Drs J Burns Amberson, Jr (Fellow), New York, O H Perry Pepper (Fellow), Philadelphia, Henry M Thomas (Fellow and Governor), Baltimore, James E Paulin (Fellow), Atlanta and Chester S Keefer (Fellow), Boston, Members of the Council, Dr George Morris Piersol (Fellow), Philadelphia, Alternate Delegate to the Executive Committee of the Congress, Dr Richard A Kern (Fellow), Philadelphia, member of the Committee on Arrangements.

Among the officers of the American Association of Pathologists and Bacteriologists were Dr Earl B McKinley (Fellow), Washington, D C, Vice President, Dr Howard T Karsner (Fellow), Cleveland, Ohio, Secretary, Dr C V Weller (Fellow), Ann Arbor, Member of the Council, Lt Col George R Callander (Fellow), M C, U S A, Delegate to the Executive Committee of the Congress, Dr Ward J MacNeil (Fellow), New York, Alternate Delegate.

Dr Elmer L Sevringhaus (Fellow), Madison, Wis, was a guest speaker at the ninety-eighth annual meeting of the Illinois State Medical Society at Springfield, May 17-19, his subject being "Pituitary Therapy in General Practice"

Among the guest speakers at the one hundred and forty-seventh annual meeting of the New Hampshire Medical Society at Manchester May 17-18 were Dr Walter

Bauer (Fellow), Boston, "Treatment of Arthritis", Dr Donald S King (Fellow), Boston, "Cancer of the Lung", and Dr Frederick T Lord (Fellow), Boston, "Treatment of Pneumonia"

Among the guest speakers at the annual meeting of the Medical Society of New Jersey, held at Atlantic City, May 17-19, were Dr Josephine B Neal (Fellow), New York, "Treatment of Infections of the Central Nervous System with Special Reference to Sulfanilamide", and Dr George B Eusterman (Fellow), Rochester Minn, "Newer Aspects in Etiology and Treatment of Ulcers of the Gastrointestinal Tract"

Dr William S Rude (Fellow), Ridgely, was elected a vice-president of the Tennessee State Medical Association at its annual meeting in Nashville during April

OBITUARIES

DR LEWIS BURGİN McBRAYER

Lewis Burgin McBrayer died at his home in Southern Pines, N C , April 1, 1938. He was born in Buncombe County, December 27, 1868, and his long and useful career in medicine from the time of his graduation from the Louisville (Ky) Medical College in 1889 was spent within the confines of his native State. For twenty-five years he practiced in Asheville, serving as County Coroner of Buncombe County, and City Health Officer of Asheville, becoming, in 1914, the Superintendent of the North Carolina State Tuberculosis Sanatorium, at Sanatorium, N C.

He was President of the Buncombe County Medical Society about 1900. From 1915 to 1920 he was Secretary of the Hoke County Medical Society, in 1918-19, he was Chairman of the Section on Public Health of the Southern Medical Association, in 1919 he was President of the Moore County Medical Society, in 1925-26 he was President of the Southern Conference on Tuberculosis, he was Managing Director of the North Carolina Tuberculosis Association, and President of the North Carolina Medical Society, as well as a member and President one year of the State Board of Medical Examiners, after which he became Secretary-Treasurer of the State Medical Society, and from 1921 until his retirement two years ago, he was given the title of "Honorary Secretary for Life" of this Society.

Being keenly interested in the furtherance of organized medicine, he was always vitally interested in, and a member of, his local County Medical Society, State Medical Society, the Southern Medical Association, the American Medical Association, the National Tuberculosis Association and its regional subdivisions, and the American College of Physicians, of which he became a Fellow in 1920, maintaining an active interest in all of these associations until illness incapacitated him.

In 1890, Dr McBrayer married Miss Lillian Cordie Deaver, of Asheville, of which union three children survive. Mrs Paul P McCain, wife of Paul P McCain, M D , F A C P , present Superintendent of the North Carolina State Tuberculosis Sanatorium, Lewis B McBrayer, Jr , and Reuben A McBrayer.

Dr McBrayer was actively interested in the Order of Odd Fellows, which organization gave him some of its highest honors, he finally serving in 1933-34 as Grand Marshal of the sovereign grand lodge. His civic interests embraced the Sand Hill Fruit Growers Association, of which he was President in 1922, the Chamber of Commerce of Southern Pines, the United States No 1 Highway Association, both of which latter organizations he also served as President. Dr McBrayer's outstanding contribution to the medical life of his State was his vitalizing interest and campaigns for the betterment of public health, and for the prevention and eradication of

tuberculosis In the American College of Physicians, he was so far as known the initiator of the idea of sectional meetings, when in 1930 the President of the College, the Secretary-General and the Executive Secretary, on his invitation, were the guests of the Fellows of the State at a luncheon during the meeting of the State Society at Pinehurst

In Dr McBrayer's death, his community, State and the country at large, have lost an enthusiastic, tireless worker in the field of preventive medicine

C H COCKE, M D ,
Governor for North Carolina

DR STEPHEN WEBB DAVIS

Dr Stephen Webb Davis, of Charlotte, N C, who died suddenly on March 16, 1938, was born September 1, 1894, the son of the late Thomas Jackson Davis and of Ella Webb Davis Dr Davis graduated from the Virginia Polytechnic Institute with a B S degree, and received the degree of M D from the University of Pennsylvania, with honors, in 1927 He served as Resident Physician at the University Hospital, in Philadelphia, and pursued postgraduate studies at the Mayo Clinic, the Government Research Station, at Beaufort, N C, and other places Prior to entering medicine, Dr Davis served as First Lieutenant of the 11th Cavalry, U S Army, during the World War, being stationed in the West and on the Mexican border

He was a member of Sigma Chi and Phi Chi (medical) fraternities, of the Mecklenburg County Medical Society, the North Carolina State Medical Society, the Tri State Medical Society of the Carolinas and Virginia, the Southern Medical Association, a Fellow of the American Medical Association, member of the American Heart Association, and became a Fellow of the American College of Physicians in 1936 He belonged to the Rotary Club of Charlotte, and to the Westmoreland Club of Richmond

In June 1935, he married Miss Kate Jones, of Summerville, Ga, and leaves his wife and one daughter, born March 9, 1938

Dr Davis was largely interested in the progressive phases of Internal Medicine, developing, some years ago, an oxygen service, available to his colleagues, and lately was tremendously interested in peripheral vascular disease, equipping himself with all the modern instruments used in these conditions He was an earnest student, an interested and zealous physician, and attempted to keep himself in the forefront of progress in his chosen field

His sudden and unexpected death cut short what might well have been a very brilliant career in internal medicine

C H COCKE, M D ,
Governor for North Carolina

MINUTES OF THE GENERAL BUSINESS MEETING

NEW YORK, N Y, APRIL 7, 1938

The Annual Business Meeting of the American College of Physicians was held at the Waldorf-Astoria Hotel, New York City, April 7, 1938. The meeting was called to order at eleven-thirty o'clock by Dr. James H. Means, President.

Abstracted Minutes of the last Annual Business Meeting were read by the Executive Secretary, Mr. E. R. Loveland, which, upon motion duly seconded and carried, were accepted as read.

The Treasurer, Dr. William D. Stroud, reported that the finances of the College were in a satisfactory state, and that the accounts had been examined and found correct by a Certified Public Accountant. He reported that on December 31, 1937, the total assets of the College, according to book value, amounted to \$205,383.47, of which \$64,534.27 was in the Endowment Fund and \$140,849.20 was in the General Fund, \$63,308.98 represented the book value of investments in the Endowment Fund, the balance of the Fund being in cash. \$64,941.60, according to book value, of the General Fund was invested in securities, the balance being represented partly in cash (\$2,891.75), partly in the College Headquarters (\$57,582.45), and partly in other assets as will be disclosed in the detailed financial reports following these Minutes. The Treasurer further referred to the detailed statements which hereafter follow.

Upon motion duly seconded and carried, the report of the Treasurer was accepted. The Executive Secretary, Mr. E. R. Loveland, presented the following report:

"During the summer and early autumn of 1937, a completely new and revised Directory of the American College of Physicians was compiled and published. Under the direction and recommendations of the Board of Governors and the Board of Regents the form of the Directory was somewhat changed, making it more informative and more practical.

"An extension of the activities of the College included the organization of Postgraduate Courses, restricted to members, given during the two weeks preceding the Annual Session. Although the project was started rather late and the final bulletins of the courses distributed only a month in advance of the Annual Session, there were formally registered 55 student-physicians in Course No. 1, in 'General Medicine,' at Harvard University Medical School, 27 student-physicians for Course No. 5, in 'General Medicine,' at the New York Post-Graduate Medical School and Hospital, 25 student-physicians for Course No. 6 'Cardiovascular Diseases' at the University of Pennsylvania Graduate School of Medicine, and 13 student-physicians for Course No. 7 'Gastro-Intestinal Diseases' also at the University of Pennsylvania Graduate School of Medicine.

"The Committee on Postgraduate Education, provided for by the Board of Regents, and appointed by the President, will continue its survey of graduate educational facilities in this country, and will also prepare a program of graduate courses for members of the College, the courses to be given in centers in or near-by the next meeting city. Full information will be published at the appropriate time in the ANNALS OF INTERNAL MEDICINE.

"The Twenty-Second Annual Session of the College in New York City has marked a high spot in the entire list of the Sessions of the College. The President, the General Chairman, the Vice Chairman and the local Committees have done a tremendous amount of work, and given the meeting much thought, which has resulted in a program second to none. The success of the meeting is attested to by the enthusiastic reports of our members and by the largest member regis-

tration at any Annual Session. The general registration was 2,228, with 319 visiting ladies, making a total of 2,547. The Round Table Conferences proved tremendously popular, with the result that we were unable to accommodate a great many of the members desiring tickets. No other innovation in the annual program has proved so popular.

"The attention of members is particularly called to the very high type of our Technical Exhibits this year, and that the number of exhibits has been reduced. The exhibits are being restricted to those having a direct relation to Internal Medicine and its allied specialties, many irrelevant and miscellaneous commercial exhibits have been eliminated. It is felt that exhibitors should be present primarily to give information and service, and not especially to make direct sales. The College desires to make its Commercial Exhibits scientific in character, and to enhance their value to its members. The revenue from exhibits goes a long way toward paying the expenses of the Annual Sessions; therefore, we owe the exhibitors our courteous attention. Members are urged to visit the various booths, for the exhibitors will be appreciative of the fact that the College members are sufficiently interested to examine the displays on which they have spent so much time and expense in preparation.

"The College accounts, according to our universal custom, have been audited by a Certified Public Accountant, and all the statements have been presented and approved by the Finance Committee and the Board of Regents. Through the cooperation of the Treasurer and the Secretary-General, and the help of a competent staff, the work in the Executive Offices of the College has been carried on with as great dispatch, promptness and efficiency as possible.

"In conclusion, I want to remind you again that we are always happy to have members visit us at our Headquarters in Philadelphia. We are gratified that so many have come during the past year, and any service we can perform is considered a privilege."

By motion duly seconded and carried, the report of the Executive Secretary was approved.

The Secretary-General, Dr. George Morris Piersol, presented the following report:

"The total membership of the American College of Physicians at this date is approximately as follows:

2 Masters
2,820 Fellows
1,080 Associates
<hr/>
3,902 Total

"During the past year, since our last Annual Session, 199 have been elected to Fellowship and 275 to Associateship. All but a very few of those elected to Fellowship were advanced from Associateship.

"Since the last Annual Session, we have lost through death, 58 members, consisting of 1 Master, 47 Fellows and 10 Associates.

"4 resignations of Fellows and 10 resignations of Associates, the latter due primarily to inability to qualify for Fellowship, have been accepted.

"All but about 7 per cent of those elected to Associateship five years ago qualified for Fellowship.

The number who have taken advantage of Life Membership has been steadily growing. Since the last Annual Session, 22 have subscribed to Life

Membership, making a grand total of 101. However, due to deaths of 4 Life Members, there remain 97. The names of the Life Members of the College are not only entered in the Directory of the College, but their names appear on the Life Membership Scroll, which is exhibited in the College Booth, space No. 36, in the Exhibit Room."

Upon motion duly seconded and carried, the report of the Secretary-General was accepted.

On behalf of the Board of Regents, in consideration of his services as President of the College, the Secretary-General, Dr. Piersol, presented to the outgoing President of the American College of Physicians, Dr. James H. Means, a silver, engraved, ferruled Gavel. Dr. Means accepted the Gavel and expressed his deep appreciation therefor.

At this point, Dr. Means called upon the incoming President, Dr. William J. Kerr, to take over the chairmanship of the meeting.

Dr. Kerr, in taking the chair, addressed the College as follows:

"I feel very humble in standing before you today to accept this high office in the College. It is a little more than a year ago when I began to receive some letters from friends congratulating me upon my election, or selection for the Presidency of the College. I had not seen notice in the *ANNALS*. That was the first intimation that any such honor could ever come my way. I must say that I was greatly surprised and I still don't understand.

"During this year of preparation for the job which lies ahead, I have felt a good deal of temerity in assuming the position, and when I have thought of the very distinguished men who have preceded me in this position and noted their accomplishments, I had hoped that I might be able to rise to the occasion.

"If you do not mind some references which I may now make, and not in a facetious mood, because this is a very serious moment in my life, I would like to liken the College to a certain long-necked bird, a land bird, if you will, one which goes rather steadily in a forward direction but with a long neck and head on the end which may be represented by your President, moving about a little here and there from side to side and up and down, but still the old bird moving steadily forward.

"This is a ground bird and the wings are not developed for flight. The chief organ of this bird is the gizzard, which accepts all manner of things which are provided and brought before it, and this is represented by our honorable Board of Regents and Governors who have to pass upon many and sundry things presented, and I must say through my brief experience on this Board that I never saw a group of men who could master problems in a more efficient manner.

"The plumage of this bird is represented by the Fellows and Associates of the College who can be recognized throughout the length and breadth of our land, including Canada and other countries near-by, because of their outstanding accomplishments which everyone in the community can well recognize.

"The chief means of defense of this particular bird is the long leg with strong toes which is provided only for a frontal attack. This bird cannot kick backwards, but only by a frontal attack can it meet its enemies and meet the problems which arise, and we are, I think, hoping that in the College we may be able to continue to anticipate danger ahead or problems ahead and meet them squarely when they come.

"Through the great speed of this bird, it has not been necessary to prepare defenses toward the rear. I may say, so far as I can understand the position of the College in the country today, we are rapidly outstripping all of our competitors.

"By now, I think you will recognize that this bird is a male, and since it is the custom among this species for the male to sit on the nest and hatch the eggs, in our College there have been several notable hatchings, chief among them now classed as our living offspring are the ANNALS OF INTERNAL MEDICINE, the College home with its very efficient staff presided over by Mr Loveland, the American Board of Internal Medicine, not yet full grown but developing well and rapidly, for the certification of internists in this country, then our educational features, chief among which during the past many years have been our Annual Sessions, and more recently the regional meetings throughout the country

"During the last year, we have added the postgraduate effort in the College and from the response which we had this year, even though we had a late start, we are encouraged to believe that this may prove to be one of the most successful and helpful of our endeavors for the membership in the College. It shows an abiding interest in keeping up that which has always distinguished the members of the profession in our special field

"We are hoping during the next year to increase our activities in this direction and perhaps to make some surveys in cooperation with other agencies on the possibilities for postgraduate instruction in this country

"It is hoped, in returning to the bird, that your President as the temporary and roaming head of this great organism may be able to keep his head out of the sand. He is a little beyond the place of the shifting sands in this country today, but it is to be hoped that he will keep awake to situations arising in the country

"If I can bring to the College the spirit of our last and rapidly diminishing frontier in the West, I shall be very happy. If the impressive water falls, the giant peaks and trees of the West have any influence upon land, then I hope that I may be able to translate some of it into activity upon behalf of the College as a whole

"There are two things which are very close to my heart in relation to the College. One of them is the matter of postgraduate training upon which we have already embarked, but in a very small way. There is another matter with respect to the dues. We hope that after due deliberation we may find some way to reduce the annual dues for members in the College. It may not be much, but we hope that it may be able to be accomplished

"In concluding these remarks, I wish to assure you that I shall labor diligently for the whole College, and I hope that I shall not let you down during my year in office. Thank you!"

Upon motion duly seconded and carried, it was

Resolved, that in accordance with the present By-Laws of the American College of Physicians and directions of the Board of Regents at a regular meeting held on April 18, 1937, and in accordance with the publication of such proposed amendment to the members in accordance with the present By-Laws, an addition shall be made to the By-Laws, Article IV, Section 1, as an additional paragraph, as follows

"Any member of the Board of Governors unable to attend the Annual Session shall appoint as his alternate, with all the privileges of a Governor, a Master or Fellow of his district who will be in attendance at that Session. Upon presentation to the Chairman of the Board of Governors of a certificate of appointment, the alternate shall be recognized and act in the full capacity of Governor for the Session to which he has been appointed. The same alternate shall not be appointed for more than two consecutive years"

President Kerr then called for a report of the Committee on Nominations by the Chairman, Dr Jonathan C Meakins, whose report herewith follows

"Mr President

I beg to report on behalf of the Nominating Committee

In accordance with the By-Laws, Article I, Section 2, we submit the following names

(A) For the Elective Offices

<i>President-Elect</i>	O H Perry Pepper, Philadelphia, Pa
<i>First Vice-President</i>	James B Herrick, Chicago, Ill
<i>Second Vice-President</i>	Noble Wiley Jones, Portland, Ore
<i>Third Vice-President</i>	Charles T Stone, Galveston, Tex

This list of nominees has been duly published in the ANNALS OF INTERNAL MEDICINE at least one month before the present date

(B) For the Board of Regents

For the Term Expiring 1940

David P Barr St Louis, Mo

For the Term Expiring 1941

James E Paullin, Atlanta, Ga
Robert A Cooke, New York, N Y
Hugh J Morgan, Nashville Tenn
Ernest E Irons, Chicago, Ill
D Sclater Lewis, Montreal, Que

(C) For the Board of Governors

For the Term Expiring 1940

Eugene H Drake	MAINE—Portland
M D Levy	TEXAS—Houston

For the Term Expiring 1941

James F Churchill	SOUTHERN CALIFORNIA—San Diego
James Waring	COLORADO—Denver
Francis G Blake	CONNECTICUT—New Haven
Wallace M Yater	DISTRICT OF COLUMBIA—Washington
Samuel E Munson	SOUTHERN ILLINOIS—Springfield
Robert M Moore	INDIANA—Indianapolis
Thomas Tallman Holt	KANSAS—Wichita
William B Breed	MASSACHUSETTS—Boston
Warren Thompson	NEBRASKA—Omaha
Leander A Riely	OKLAHOMA—Oklahoma City
Nelson G Russell	WESTERN NEW YORK—Buffalo
R R Snowden	WESTERN PENNSYLVANIA—Pittsburgh
Edward L Bortz	EASTERN PENNSYLVANIA—Philadelphia
John L Calene	SOUTH DAKOTA—Aberdeen
J Owsley Manier	TENNESSEE—Nashville
Louis E Viko	UTAH—Salt Lake City
Harry L Arnold	HAWAII—Honolulu
J H Holbrook	ONTARIO—Hamilton, Canada
C F Moffatt	QUEBEC—Montreal, Canada
William M James	PANAMA and the CANAL ZONE "

President Kerr then asked if there were other nominations to be made from the floor. There were none, and upon motion duly seconded and unanimously carried, it was

Resolved, that the nominations be closed and that the secretary cast the ballot for the election of the nominees presented by the Nominating Committee.

President Kerr then asked for the presentation of other business, whereupon the following resolution, offered by Dr. Jonathan C. Meakins, was duly seconded and unanimously carried with a rising vote:

Resolved, that the cordial thanks of the American College of Physicians be extended to the Retiring President, Dr. James H. Means, to the General Chairman, Dr. James Alex. Miller, and to the Vice Chairman and members of his various committees, individually and collectively, for their faithful work in the preparation and conduct of the New York Session, to the Ladies Entertainment Committee for their efficiency and courteous entertainment of our visiting ladies, to the medical schools and hospitals of New York City for putting their facilities at the disposal of the College, and for their helpful participation, to the New York Convention Bureau and its Director for their assistance, and the Waldorf-Astoria Hotel and its Convention Manager for their cooperation.

Adjournment

EXECUTIVE SECRETARY'S REPORT

1937

The auditor's report of his examination of the accounts of the College is hereto attached. Even with added activities affecting the finances of the College, such as the gift of one thousand dollars to the National Conference on Nomenclature of Diseases and the writing off of one thousand dollars as depreciation on the Headquarters Building, as directed by the Board of Regents, the surplus is still favorable as below indicated:

1935 Surplus	\$ 17,182 09
1936 "	24,946 53
1937 "	23,765 75

The 1937 surplus was distributed as follows:

Endowment Fund	\$ 2,749 45
General Fund	21,016 30
	<hr/>
	\$ 23,765 75
	<hr/>

The total principals of the two Funds on December 31, 1937, were:

Endowment Fund	\$ 64,534 27
General Fund	140,849 20
	<hr/>
	\$205,383 47
	<hr/>

For comparison, the total assets of the College in 1926 were only \$9,000 00. The growth of the activities and services of the College has been greatly expanded during the intervening years, yet there has been built up an excellent financial foundation. Conservative policies and aggressive effort are responsible, although the general momentum and natural growth have contributed much in recent years. The

journal, ANNALS OF INTERNAL MEDICINE, was for many years the source of considerable deficits. Volume I showed but ten and three-quarters pages of paid advertising, Volume X (completed, June 1937) showed two hundred and sixty-seven pages of paid advertising. Volume I had an average circulation of 1803, Volume X, 3878. The March, 1938, issue (Vol XI, No 9) had a circulation of 4210. But the College has also given its members more as the journal grew, Volume I had 1040 pages of scientific content, Volume X, 1786 pages.

During 1937 a new and revised Directory of the College was published in accordance with recommendations of the Board of Governors and the Board of Regents. The Directory contains 621 pages, and was published at a total cost, including cost of distribution, of slightly over \$4,000.00. The cost in labor and funds is well justified by its wide use by members of the College, medical societies, medical schools, hospitals, insurance companies and other agencies.

The budgets for 1938 were approved in detail by the Board of Regents December 12, 1937.

Respectfully submitted,

(Signed) E R LOVELAND,
Executive Secretary

January 1, 1938

H I MACLEAN
309 Valley Road
Llanerch, Pa

March 4, 1938

To the Board of Regents

American College of Physicians, Inc
Philadelphia, Pa

Mr E R Loveland, Executive Secretary

Dear Sirs

I have examined the accounts of the

AMERICAN COLLEGE OF PHYSICIANS, INC

for the year ended December 31, 1937, and the accompanying statements, including the Balance Sheet at December 31, 1937, the analyses of the General Fund and the Endowment Fund and the Detailed Statement of Operations for the year ended December 31, 1937, are in accordance with the books of account and in my opinion set forth correctly the financial position at December 31, 1937, and the results of operations for the calendar year ended December 31, 1937, subject to the following comments:

Cash The cash was properly accounted for. The following is a statement of the cash in the various depositories:

Girard Trust Company, Philadelphia	\$2,313 75
Provident Trust Company, Philadelphia	861 47
Royal Bank of Canada, Montreal	741 82
	<hr/>
	\$3,917 04
	<hr/>

The amount of cash in closed banks at January 1, 1937, was \$6,292 39, during the year a liquidating dividend amounting to \$583 06 was received, which reduced the amount to \$5,709 33, as shown by the following schedule

	<i>Balance Jan 1, 1937</i>	<i>Liquidating Dividend</i>	<i>Balance Dec 31, 1937</i>
Bank of Pittsburgh, Pittsburgh	\$1,461 97		\$1,461 97
Exchange National Bank, Pittsburgh	1,749 20	\$583 06	1,166 14
Highland National Bank, Pittsburgh	3,081 22		3,081 22
	<u>\$6,292 39</u>	<u>\$583 06</u>	<u>\$5,709 33</u>

Accounts Receivable The accounts receivable were examined and found to be less than one year old and appear to be good and collectible. The detailed accounts receivable were in agreement with the control account. No requests for confirmation of the accounts were mailed.

Investments The securities were accounted for by direct correspondence and the income for the period under review was verified.

General The increase in the amount of the Endowment Fund and the General Fund during the year 1937 is as follows

	<i>Balance Jan 1, 1937</i>	<i>Net Increase</i>	<i>Balance Dec 31, 1937</i>
Endowment Fund	\$ 61,784 82	\$ 2,749 45	\$ 64,534 27
General Fund	119,832 90	21,016 30	140,849 20
	<u>\$181,617 72</u>	<u>\$23,765 75</u>	<u>\$205,383 47</u>

In accordance with the instructions of the Executive Secretary, the prepaid insurance at December 31, 1937, was not set up as a deferred expense, the other deferred and accrued items were verified, the charges to the College Headquarters account were examined, and in my opinion appear to be proper charges to this account, the charges to the Furniture and Equipment accounts represent proper additions to this account and the allowance for depreciation appears to be adequate, a depreciation reserve account has been set up for the new building in accordance with the action of the Board of Regents at the meeting on December 12, 1937, which provided that depreciation on the building should be taken into account at the rate of \$1,000 00 per year, the footings and extensions of the inventory were verified, all ascertainable liabilities have been included in the balance sheet, all recorded receipts from dues, initiation fees, exhibits, advertising, sales of publications, etc., were properly deposited in bank and all disbursements, as indicated by the vouchers, cancelled checks and bank statements, were properly recorded in the books of account.

Very truly yours,

(Signed) H I MacLEAN,
Certified Public Accountant

GENERAL FUND

For the Year Ended December 31, 1937

Balance, January 1, 1937	\$119,832 90
Less	
Transfer to Endowment Fund of the Initiation Fees of Life Members	730 00
	<u>\$119,102 90</u>

Summary of Operations for the Year ended December 31, 1937

Income

Annual Dues	\$24,695 08	
Subscriptions, ANNALS OF INTERNAL MEDICINE	24,649 79	
Advertising, ANNALS OF INTERNAL MEDICINE	8,863 51	
Initiation Fees	11,616 50	
Income from Invested Funds (General)	2,164 16	
Exhibits, 21st Annual Session	9,832 66	
Guest Fees, 21st Annual Session	421 00	
Other Income	351 26	
Profit on Investments of General Fund sold (net)	1,420 51	\$84,014 47

Expenses

Salaries	\$19,533 78	
Postage, Telephone, Telegraph	3,399 04	
Office Supplies and Stationery	1,054 76	
Printing	19,562 84	
Traveling Expenses	4,342 72	
College Headquarters		
Maintenance	\$2,109 16	
Taxes	1,253 07	
Insurance	86 77	
Miscellaneous	100 00	3,549 00
Depreciation on Building, Furniture and Equipment	1,847 02	
Grant to the National Conference on Nomenclature of Diseases	1,000 00	
Printing 1937 Directory	4,039 31	
Other Expenses		
21st Annual Session	2,260 49	
ANNALS OF INTERNAL MEDICINE	257 51	
Miscellaneous	1,421 70	3,939 70
		<u>62,268 17</u>

Net Income for the Year Ended December 31, 1937 21,746 30

Balance, December 31, 1937 \$140,849 20

ENDOWMENT FUND

For the Year Ended December 31, 1937

Principal Account, January 1, 1937	\$61,784 82
Add	
Life Membership Fees received during 1937	\$2,270 00
Transfer of Initiation Fees of New Life Members from General Fund	730 00
	<u>3,000 00</u>
Deduct	
Loss on Sale of Investments	250 55
Principal Account, December 31, 1937	<u>\$64 534 27</u>

*Income Account

Income from Investments earned during 1937	\$ 2,428 54
Deduct	
Research Fellowships	\$2,330 25*
John Phillips Memorial Prize	98 29
	<u>2,428 54</u>

* \$69 75 additional was expended from the General Fund during 1937 on account of the Research Fellowships

DETAILED STATEMENT OF OPERATIONS

For the Year Ended December 31, 1937

General Income

Annual Dues	\$24,695 08	
Initiation Fees	11,616 50	
Income from General Fund Investments	2,164 16	
Profit from Sales of Keys, Pledges and Frames	181 94	
Profit on Investments of General Fund sold (net)	1,420 51	
Dividend on Insurance Deposit	60 00	\$40,138 19

Twenty-first Annual Session

Expenses

Salaries	\$ 4,049 99	
Communications (Postage, Telephone, etc)	480 17	
Office Supplies and Stationery	144 65	
Printing	1,061 11	
Traveling Expenses	2,418 32	
Other Items		
Advertising	\$ 100 70	
Badges	191 50	
Convocation	492 59	
Ladies Committee	502 81	
Reporting	90 00	
Smoker	342 27	
Other Miscellaneous Items	540 62	2,260 49

10,414 73

Income

Exhibits (Net)	\$ 9 832 66	
Guest Fees	421 00	
Profit on Banquet	109 32	10,362 98

Net Expenses of Annual Session

51 75

Annals of Internal Medicine

Income

Subscriptions		
Volume I	\$ 14 27	
Volume II	10 49	
Volume III	9 02	
Volume IV	9 62	
Volume V	7 63	
Volume VI	12 68	
Volume VII	28 75	
Volume VIII	31 45	
Volume IX	90 07	
Volume X	1,369 22	
Volume XI	23,066 59	\$24,649 79

Advertising (Net)

Volume X	\$ 4,243 94	
Volume XI	4,619 57	8,863 51

\$33,513 30

Expenses

Salaries	\$ 6,310 74	
Communications (Postage, Telephone, etc)	1,195 03	
Office Supplies and Stationery	303 89	
Printing	17,443 92	
Miscellaneous	156 88	
Allowances, Adjustments and Purchases	100 63	25,511 09

Net Profit on ANNALS OF INTERNAL MEDICINE

8,002 21

Total Income

\$48,140 40

*Executive Secretary's Office**Expenses*

Salaries	\$ 9,173 05	
Communications (Postage, Telephone, etc)	1,723 84	
Office Supplies and Stationery	606 22	
Printing	1,057 81	
Maintenance	32 73	
Traveling Expenses	1,924 40	
Fee to Custodian of Securities	151 13	
Miscellaneous Items	494 09	15,163 27

College Headquarters

Maintenance	\$ 2,109 16	
Taxes	1,253 07	
Insurance	86 77	
Miscellaneous	100 00	3,549 00

Other Expenses

Investment Counsel Service		200 00	
ANNALS OF INTERNAL MEDICINE Distributed Free to Life Members		474 00	
Printing 1937 Directory, net		4,039 31	
Grant to the National Conference on Nomenclature of Disease		1,000 00	
Research Fellowships (amount not provided by Income of Endowment Fund)		69 75	
Depreciation			
Building	\$ 1,000 00		
Furniture and Equipment	847 02	1,847 02	26,394 10

Net Income for the Year Ended Dec 31, 1937

\$21,746 30

INVESTMENTS

December 31, 1937

<i>Par Value</i>		<i>Endowment Fund Securities</i>	<i>General Fund Securities</i>
	<i>Bonds</i>		
\$ 5,000	Bell Telephone of Canada, 5s, 1955	\$ 5,562 50	
2,000	Canadian National (West Indies) SS Co, Ltd, 5s, 1955	2,040 00	
5,000	Cities Service Co, 5s, 1950		\$ 4,075 90
1,000	City of Montreal, 5s, 1956	1,071 30	
5,000	Columbia Gas and Electric Corp, Deb, 5s, 1961		4,956 25
5,000	Commonwealth Edison Co, First, Series "F," 4s, 1981	4,744 35	
5,000	Government of the Dominion of Canada, 4s, 1960	4,662 50	
2,000	Great Northern Railway Co, Series "H," 4s, 1946	2,100 45	
3,000	Great Northern Railway Co, Series "H," 4s, 1946		2,910 45
5,000	New York Central RR, 3¾s, 1946	4,900 00	
1,000	North American Edison Co, Deb, Series "A," 5s, 1957		1,007 75
5,000	Northern States Power Co, 1st & Ref Mort, 3½s, 1967	4,806 25	
2,000	Ohio Edison Co, 1st Mort, 4s, 1965	2,115 00	
3,000	Ohio Edison Co, 1st Mort, 4s, 1965		3,172 50
5,000	Pennsylvania Railroad, Gen, 4¼s, Series "E," 1984		5,013 10
2,000	Port of New York Authority, New York-New Jersey Interstate Bridge, 4½s, Series "B," 1952	2,042 20	
2,000	Port of New York Authority, New York-New Jersey Interstate Tunnel, 4¼s, Series "E," 1958	2,065 40	

MINUTES OF THE GENERAL BUSINESS MEETING

5,000	Southern Kraft Corp , 1st Leasehold & Gen Mort , 4 $\frac{1}{4}$ s, 1946		5,062 50	
5,000	Southern Pacific Co , 3 $\frac{3}{4}$ s, 1946		5,008 65	
5,000	Texas and Pacific Railway, Gen and Ref , B, 5s, 1977	5,313 40		
2,000	U S Treasury, 4s, 1954	1,998 13		
20,000	U S Treasury, 3 $\frac{1}{4}$ s, 1945	19,887 50		
5,000	Virginia Public Service, 5 $\frac{1}{2}$ s, 1946		5,133 65	
<u>\$100,000</u>	<u>TOTALS, Bonds</u>	<u>\$63,308 98</u>	<u>\$36,340 75</u>	<u>\$ 99,649 73</u>

<i>Shares</i>	<i>Stocks</i>			
50	Atchison, Topeka and Santa Fe		\$ 4,970 75	
30	Caterpillar Tractor Co		3,014 40	
50	Chase National Bank of New York		2,775 00	
50	Continental Can Co , Inc		5,125 00	
150	Pacific Gas & Electric Corp		4,640 50	
20	J C Penny Co		1,375 30	
50	Timken Roller Bearing Company		3,407 25	
50	Union Carbide & Carbon Corporation		3,292 65	
	<u>TOTAL, Stocks</u>		<u>\$28,600 85</u>	
	<u>TOTAL, Investments</u>	<u>\$63,308 98</u>	<u>\$64,941 60</u>	<u>\$128,250 58</u>

REPORT ON REGISTRATION OF THE
TWENTY-SECOND ANNUAL SESSION
OF THE
AMERICAN COLLEGE OF PHYSICIANS
New York, N Y April 4-8, 1938

Below appears a distribution of the registration at the New York Session of the College. The member attendance was the highest at any meeting in the history of the College. The guest attendance was restricted very largely to guest clinicians and speakers, since the physical facilities could not accommodate the large number of guests that would attend if admission were open to all members of the local county medical societies in the district.

The New York registration compares with previous registrations as follows:

<i>Session</i>	<i>Members</i>	<i>Guest Physicians</i>	<i>Students</i>	<i>Ex- hibitors</i>	<i>Guest Non- Physicians</i>	<i>Visiting Ladies</i>	<i>Total</i>
NEW YORK (1938)	1447	463	3	291	24	319	2,547
ST LOUIS (1937)	877	589	414	201	30	210	2,321
DETROIT (1936)	733	539	172	132		103	1,679
PHILADELPHIA (1935)	923	749	346	231		195	2,444
CHICAGO (1934)	690	660	420	194		121	2,085

REGISTRATION BY STATES

<i>Provinces and States</i>	<i>Members</i>	<i>Guests</i>	<i>Total</i>
<i>UNITED STATES</i>			
ALABAMA	9		9
ARIZONA	4		4
ARKANSAS	5	1	6
CALIFORNIA	26	2	28
COLORADO	11	1	12
CONNECTICUT	54	6	60
DELAWARE	7	1	8
DISTRICT OF COLUMBIA	33	3	36
FLORIDA	13		13
GEORGIA	18	1	19
IDAHO	1		1
ILLINOIS	37	12	49
INDIANA	13	2	15
IOWA	9		9
KANSAS	10		10
KENTUCKY	10	2	12
LOUISIANA	13	1	14
MAINE	12	1	13
MARYLAND	48	4	52
MASSACHUSETTS	70	18	88
MICHIGAN	60	6	66
MINNESOTA	25	8	33
MISSISSIPPI	7		7
MISSOURI	16	1	17
MONTANA	5		5
NEBRASKA	10	1	11
NEW HAMPSHIRE	5	2	7
NEW JERSEY	74	7	81
NEW MEXICO	1		1
NEW YORK	375	293	668
NORTH CAROLINA	30	3	33
NORTH DAKOTA	2		2
OHIO	77	16	93
OKLAHOMA	11	2	13
OREGON	6	3	9
PENNSYLVANIA	163	30	193
RHODE ISLAND	16	2	18
SOUTH CAROLINA	7	3	10
SOUTH DAKOTA	2		2
TENNESSEE	10		10
TEXAS	18	1	19
UTAH	3	1	4
VERMONT	3	2	5
VIRGINIA	36	1	37
WASHINGTON	5	1	6
WEST VIRGINIA	22	4	26
WISCONSIN	11	4	15
<i>CANAL ZONE</i>			
ANCON	1		1

<i>Provinces and States</i>	<i>Members</i>	<i>Guests</i>	<i>Total</i>
<i>PHILIPPINE ISLANDS</i>			
MANILA		1	1
<i>PUERTO RICO</i>			
SAN JUAN	2		2
<i>FOREIGN</i>			
<i>CANADA</i>			
ALBERTA	1		1
BRITISH COLUMBIA	1	1	2
MANITOBA	1		1
NEW BRUNSWICK	5	1	6
NOVA SCOTIA	1		1
ONTARIO	18	11	29
QUEBEC	12	1	13
SASKATCHEWAN	1		1
<i>FINLAND</i>			
HELSINGFORS		1	1
<i>HUNGARY</i>			
BUDAPEST		1	1
<i>REPUBLIC OF PANAMA</i>			
PANAMA	1		1
Total	<u>1,447</u>	<u>463</u>	<u>1,910</u>
Total Visiting Ladies			319
Total Students			3
Total Exhibitors			291
Total Guest Non-Physicians			24
GRAND TOTAL			<u><u>2,547</u></u>

LaMOTTE OUTFIT for DETERMINING SULFANILAMIDE IN BLOOD AND URINE

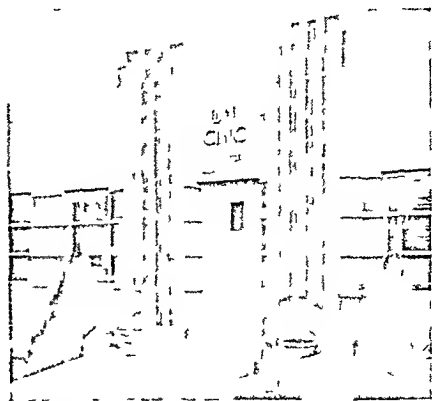
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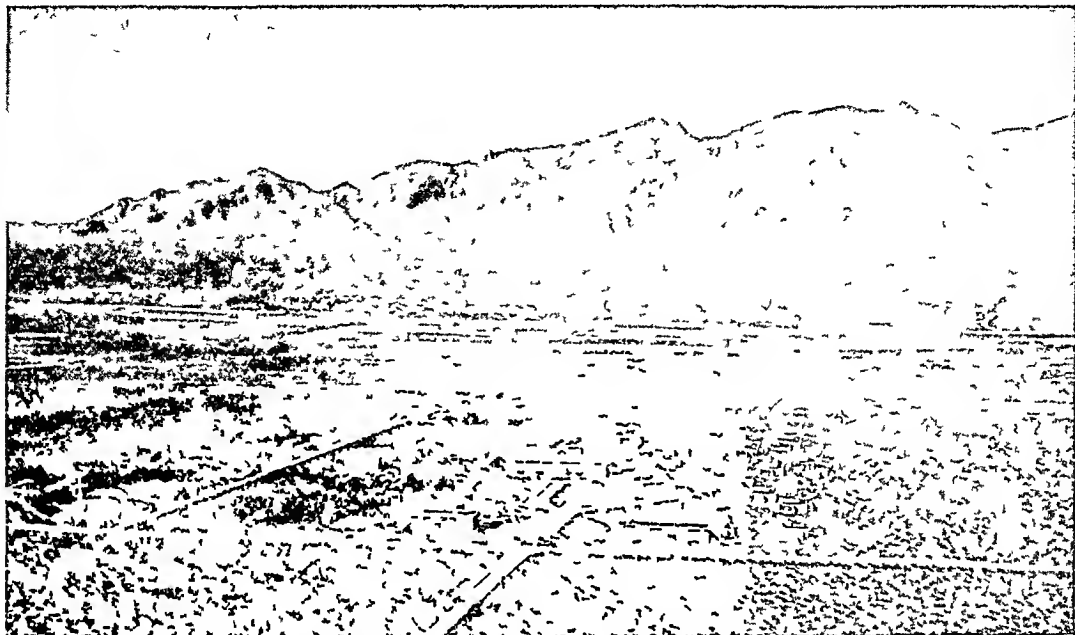


The Desert Sanatorium of Southern Arizona, Inc.

TUCSON, ARIZONA

ROLAND DAVISON, M D , *Medical Director*

TONEY A HARDY, *Business Manager*



Airplane View of the Sanatorium Grounds and Buildings

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3 To maintain employment for certain members of the Sanatorium staff who otherwise would not be retained during the summer months



Frasher Foto Pomona California
Administration Building

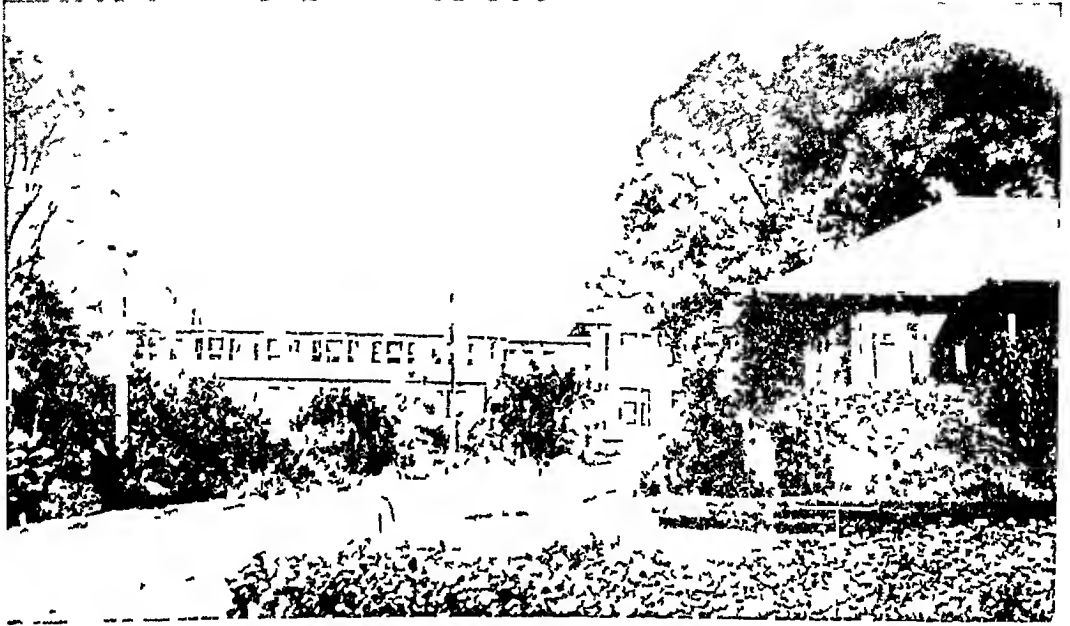


Out Patient Clinic

For further information address The Desert Sanatorium of Southern Arizona Inc , Tucson, Arizona

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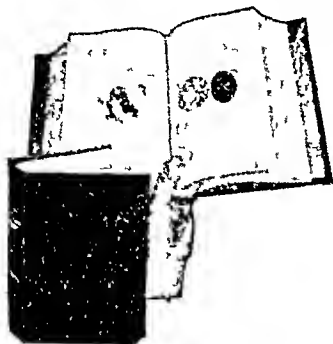
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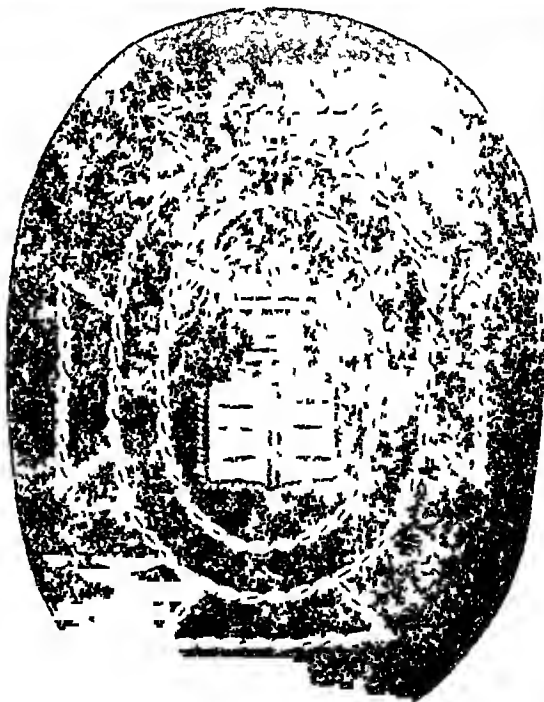
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Place of Publication—Prince and Lemon Sts., Lancaster, Pa

Editorial Office—University Hospital,
Baltimore, Md.

Executive Office—4200 Pine Street,
Philadelphia, Pa

THE ANNALS OF INTERNAL MEDICINE is published by the American College of Physicians. The contents consist of contributions in the field of internal medicine, editorials, book reviews, and a section devoted to the affairs of the College.

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